Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting information for:

A sustainable and scalable multicomponent continuous-flow process to access fused imidazoheterocycle pharmacophores

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W. J. K: Review and editing: Co-Lead, Supervision: Co-Lead, Co-corresponding author.

D. M. L: Secondary supervision: Lead, Review and editing: Co-Lead.

V. K. P: Conceptualisation: Co-Lead.

D. L. P: Conceptualisation: Co-Lead, Review and editing: Co-Lead, Supervision: Co-Lead, Co-corresponding author.

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Contents

1. General experimental information and equipment used

1.1. Solvents and reagents

Unless otherwise stated:

- Anhydrous solvents were not required, and glassware was not dried prior to use.
- All solvents and reagents were obtained from commercial suppliers, or from within GlaxoSmithKline's internal chemical storage system, and were used without further purification.
- Reactions were monitored by a combination of High Performance Liquid Chromatography (HPLC), Liquid Chromatography-Mass Spectrometry (LCMS) and Nuclear Magnetic Resonance (NMR) spectroscopy analysis techniques.

Where intermediates have been synthesised in-house, all written procedures have been provided.

1.2. Chromatography

Thin layer chromatography (TLC) was carried out with plastic-backed 50 precoated silica plates as the stationary phase (particle size 0.2 mm). Spots were visualized by ultraviolet (UV) light (λ_{max} = 254 nm or 365 nm) in all cases. Normal phase silica gel chromatography was carried out using the Teledyne ISCO CombiFlash Rf+ apparatus with RediSep silica cartridges. Reverse phase chromatography was carried out using Teledyne ISCO CombiFlash Rf+ apparatus with Biotage SNAP KPC18-HS cartridges. In each case, the size of the cartridge, and gradient of the eluent mixture used for purification is mentioned within the procedure.

1.3 Mass Directed Auto Purification (MDAP)

MDAP was carried out using a Waters ZQ MS, using an Xselect C18 column (150 mm × 30 mm, 5 µm packing diameter) and a 40 mL/min flow rate with alternate-scan positive and negative electrospray ionisation and a summed UV wavelength of 210–350 nm. Two liquid phase methods were used:

Formic: Gradient elution was performed at ambient temperature with the eluents as (A) H_2O containing 0.1% volume/volume (v/v) formic acid and (B) acetonitrile containing 0.1% (v/v) formic acid.

High pH: Gradient elution was performed at ambient temperature with the eluents as (A) 10 mM aqueous ammonium bicarbonate solution, adjusted to pH 10 with aqueous ammonia and (B) acetonitrile.

The elution gradients used were at a flow rate of 40 mL/min over 20 or 30 min depending on separation:

Method A	5-30 % B
Method B	15-55 % B
Method C	30-85 % B
Method D	50-99 % B
Method E	80-99 % B

1.4. Liquid Chromatography Mass Spectrometry (LCMS)

LCMS analysis was performed on an Acquity UPLC instrument equipped with a CSH™ C18 column (50 mm × 2.1 mm, 1.7 µm packing diameter) and micromass ZQ MS machine using alternate-scan positive and negative electrospray. Analytes were detected as a summed UV wavelength of 210-350 nm using Acquity 2998 photodiode array (PDA) and Acquity QDA mass detectors. Two liquid phase methods were used:

- **Method A – High pH (ammonium bicarbonate)**: 40 °C, 1 mL/min flow rate. Gradient elution between (A) 10 mM aqueous ammonium bicarbonate solution, adjusted to pH 10 with 0.88 M aqueous ammonia, and (B) acetonitrile. Gradient conditions began at 1% B, and increased linearly to 97% B over 1.5 min, before remaining at 97%B for 0.4 min, and then increasing to 100 %B over 0.1 min.
- **Method B – Low pH (formic acid)**: 40 °C, 1 mL/min flow rate. Gradient elution between (A) a 0.1% volume/volume (v/v) formic acid aqueous solution and (B) acetonitrile containing 0.1% volume/volume (v/v) formic acid. Gradient conditions began at 1% B, and increased linearly to 97% B over 1.5 min, before remaining at 97% B for 0.4 min, and then increasing to 100% B over 0.1 min.

1.5. Nuclear Magnetic Resonance (NMR) Spectroscopy

^{1}H and ^{13}C NMR spectra were recorded in commercially supplied deuterated solvents at ambient temperature using standard pulse methods with the following spectrometers, and associated signal frequencies: Bruker® AV-400™ (^{1}H = 400 MHz, ^{13}C = 101 MHz) and Bruker® AV-600™ (^{1}H = 600 MHz, ^{13}C = 151 MHz). Chemical shifts (δ) are reported to the nearest 0.01 ppm for ^{1}H NMR signals, and 0.1 ppm for ^{13}C NMR signals, and are relative to tetramethylsilane (TMS) reference, where δ (TMS) = 0.00 ppm. For ^{13}C NMR spectroscopic analyses where no distinct TMS peak was observed, solvent references of 49.00 (CD_3OD), 39.52 (DMSO-d_6) and 77.16 ($CDCl_3$) ppm, respectively, were used, according to the published literature.[1] All NMR analysis were performed in the following commercially supplied deuterated solvents: chloroform-*d*, methanol-d_4 and dimethyl sulfoxide-d_6. Peak assignments were made based on data derived from ^{1}H, ^{13}C, COSY, DEPT, HSQY, HMBC and NOESY analysis, where necessary. Coupling constants (*J*) are reported to the nearest 0.1 Hz for ^{1}H NMR spectroscopic analyses, and the multiplicities of signals are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sxt), broad (br.) and multiplet (m), or a combination of these descriptors for extended coupling patterns. In cases where theoretically multiple couplings are observed as a single multiplicity (including when overlapping splitting patterns are observed), an apparent (app.) descriptor is used. The number of hydrogen, carbon, or fluorine atoms (n) responsible for a signal is indicated by nH or nC, respectively.

1.6. Infrared (IR) Spectroscopy

Infa-red (IR) spectroscopy was performed using a Perkin Elmer Spectrum 1 machine. All absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

1.7. High Resolution Mass Spectrometry (HRMS)

The HRMS method combined an Ultra High Performance Liquid Chromatography (UPLC) method using an Acquity UPLC BEH C18 column with column dimensions of 100 mm × 2.1 mm (1.7 µm packing diameter), with a Waters XEVO G2-XS QTof mass spectrometer, using a positive electrospray ionisation, and a scan range of 100–1200 Atomic Mass Units (AMU). The UPLC separation was performed using the following liquid phase method:

> **Low pH (formic acid):** 50 °C, 0.8 mL/min flow rate. Gradient elution between (A) a 0.1% volume/volume (v/v) solution of formic acid in H_2O, and (B) a 0.1% volume/volume (v/v) solution of formic acid in acetonitrile. Gradient conditions began at 3% B, before the gradient increased linearly to 100% B over 8.5 min. The gradient remained at 100% B for 0.5 min, and then returned to 3% B over 0.5 min, and was held at this gradient for a further 0.5 min. The whole process required 10 min.

In all cases, the UV detection used a summed signal from a wavelength range of 210–350 nm and an injection volume of 0.2 µL was used.

1.8 High Performance Liquid Chromatography (HPLC)

HPLC analysis was carried out on an Agilent Zorbax SB-C18 machine, with column dimensions 50 × 3.0 mm (1 µm packing diameter). Analytes were measured at a UV wavelength of 220 nm. HPLC analysis was performed at 60 °C, at a 1.5 mL/min flow rate using a gradient elution between (A) 0.05% volume/volume (v/v) trifluoroacetic acid (TFA) in H_2O, and (B) 0.05% volume/volume (v/v) trifluorotoluene (TFA) in acetonitrile. Gradient conditions began at 100% A, and eluted to 95% B and 5% A over a time frame of 2.5 min. The elution composition was then maintained for 12 sec, before increasing to 100% B over 0.6 s. The elution gradient is maintained at 100% B for a further 1.29 min. The whole gradient process takes 4.0 min. The injected volume of analyte solution is 1.0 µL.

1.9 Melting Points

Melting points were recorded using a Büchi Melting Point M-565 machine. A melting point range of 40 C – 300 °C was measured, with a 5 °C/minute ramp rate.

1.10 Microwave (MW) Reactions

Reactions under microwave conditions were performed in a Biotage initiator+ microwave reactor.

1.11 Flow Reactions

Flow reactions were performed in a bespoke reactor. The reactor was made through the combination of a Syrris Asia syringe pump module, which utilised Syrris Asia green syringes (250 µL/500 µL volume syringes, which can facilitate a flow rate between 5 µL to 1.25 mL/minute/channel) with a Vapourtec RS-200 machine using a 10 mL sample loop (2 × 10 mL sample loops were used in the scale-up example). PFA tubing of outer diameter 1/8" (inner diameter 1/16") was used for the input of the Syrris module, whilst PFA tubing of 1/16" outer diameter and 1/32" inner diameter was used for the output of the Syrris module, and throughout the rest of the reactor. The tubing passed through two back pressure regulators of 75 and 40 psi (*ca.* 8.0 bar total back pressure was applied in the system). A picture of the flow setup is provided below (**Figure S1**), and this setup is also represented in the electronic line diagram (ELD) shown below (**Figure S2**).

2. Flow Reactor Diagram

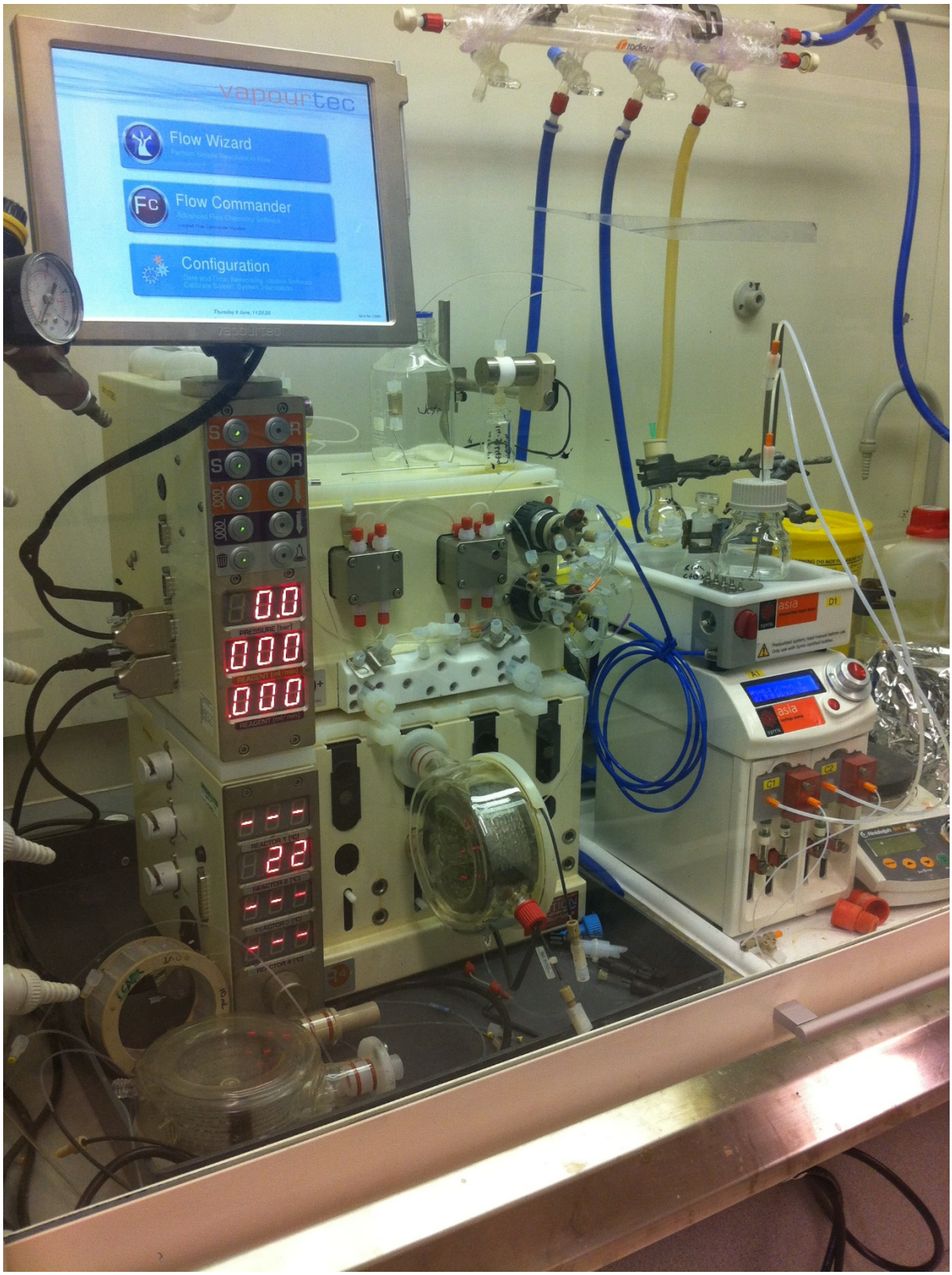


Figure S1: The bespoke flow chemistry setup used.

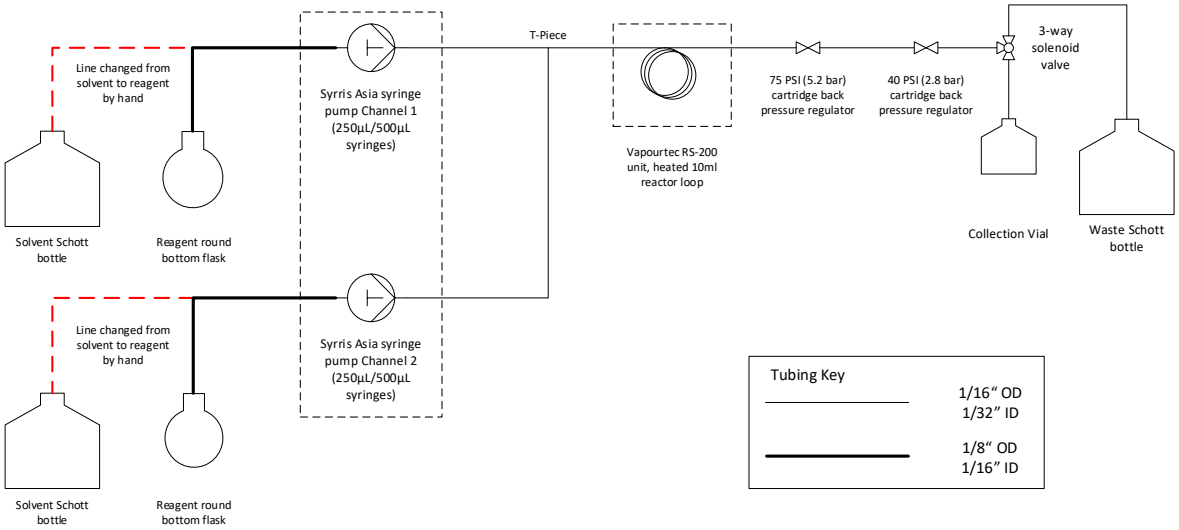


Figure S2: ELD representation of the flow equipment used.

3. Flow reactor volumes

Calculations of the reactor volume of the flow setup were made by filling the flow reactor with toluene, before pumping a fluorescent Rose Bengal aqueous solution into the reactor, and observing the residence times in different parts of the reactor at a flow rate of 0.1 mL/min/line. Schematics detailing these reactor volumes are shown below for both the usual setup of the reactor (using 1 × 10 mL reaction loop, **Figure S3**) as well as for the scale-up example (using 2 × 10 mL reaction loops, **Figure S4**).

Standard setup for reactions:

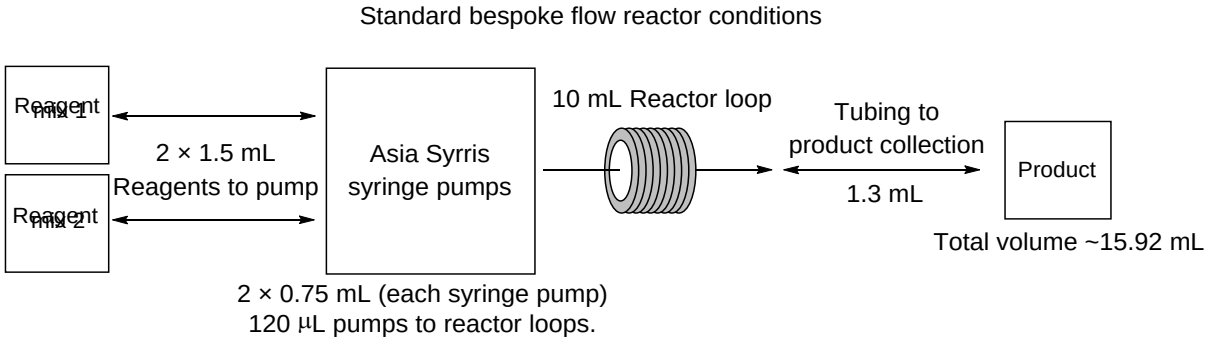


Figure S3: Schematic representation for the usual 10 mL reaction volume setup used.

Scale-up reaction setup:

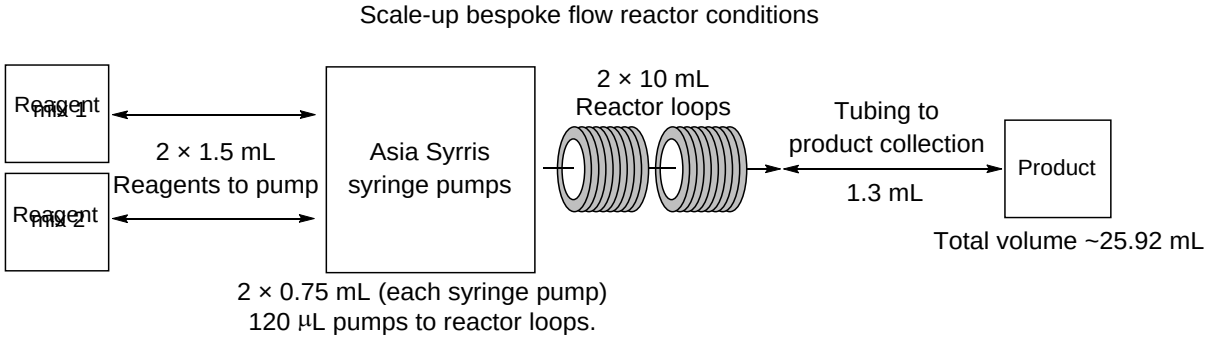


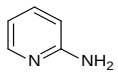
Figure S4: Schematic representation for the scale-up 20 mL reaction volume setup used.

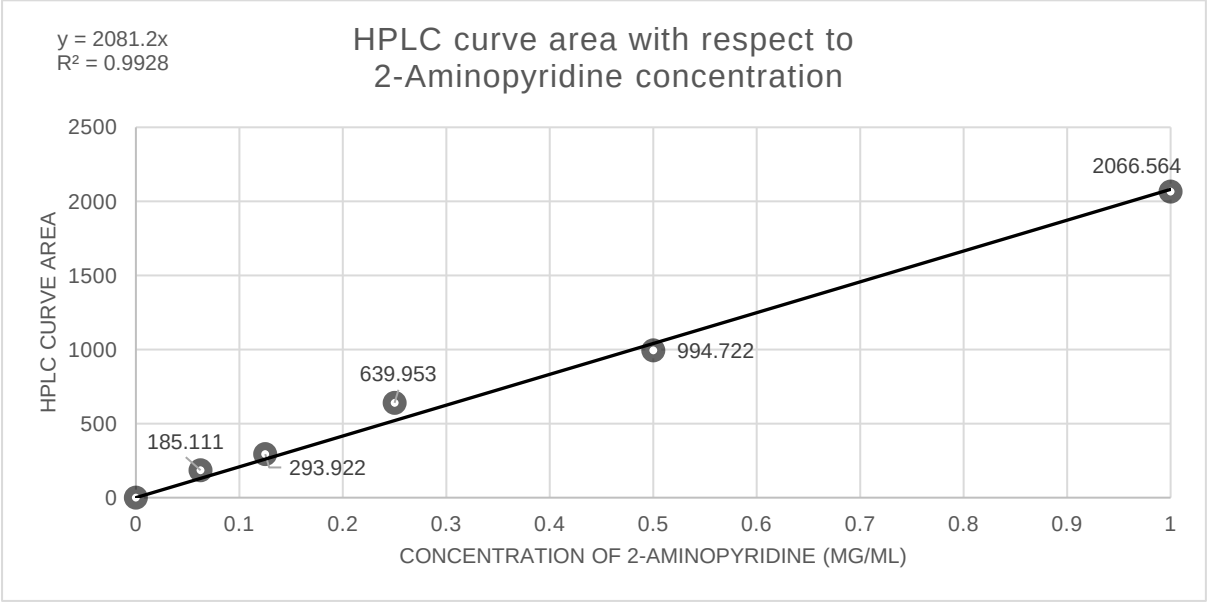
4. HPLC concentration gradients and associated procedure

To prepare a HPLC concentration gradient for each amidine starting material, the following procedure was performed:

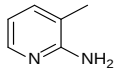
HPLC concentration gradient general procedure: 50.0 mg of the amidine of interest was dissolved in methanol to generate a 50.0 mL total solution volume of 1 mg/mL concentration. From this stock solution was separately taken 1.00 mL, 0.50 mL, 0.25 mL, 125 µL and 62.5 µL samples, which were each placed into HPLC vials. To these vials were added 0 mL, 0.50 mL, 0.75 mL, 0.875 mL, and 0.9375 mL methanol, respectively, to generate 1 mL solutions of varying concentrations. For each amidine, these concentration values were then plotted against the observed HPLC AUC data to generate concentration gradients. Only data with an $R^2 \geq 0.99$ was accepted. If data was insufficiently uniform, the procedure was repeated.

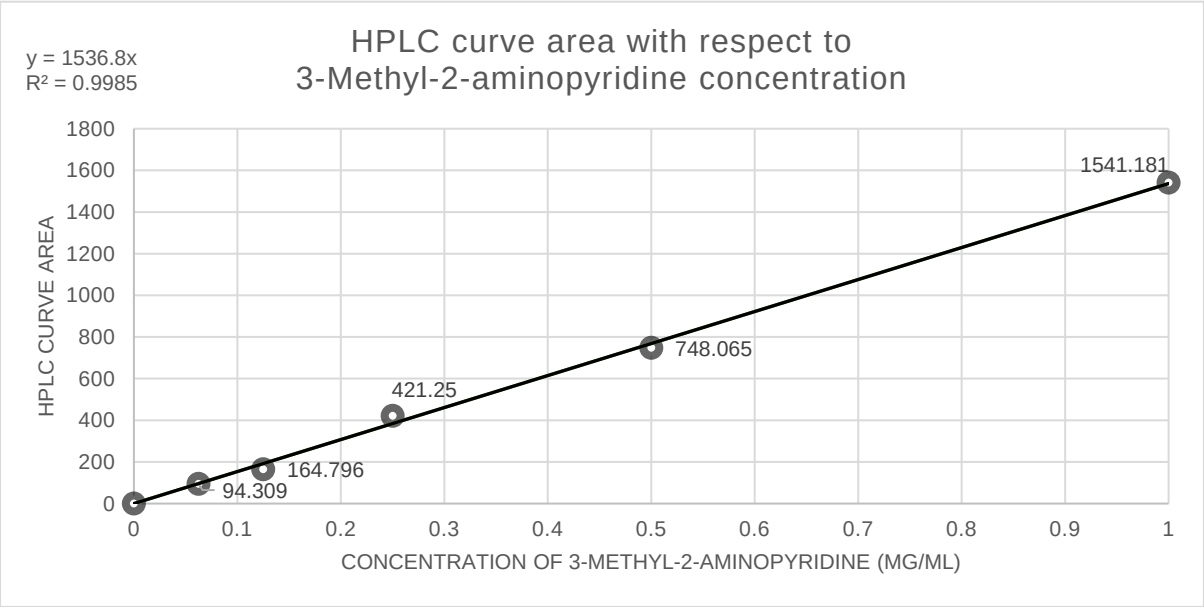
2-Aminopyridine 1a



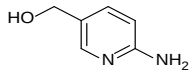


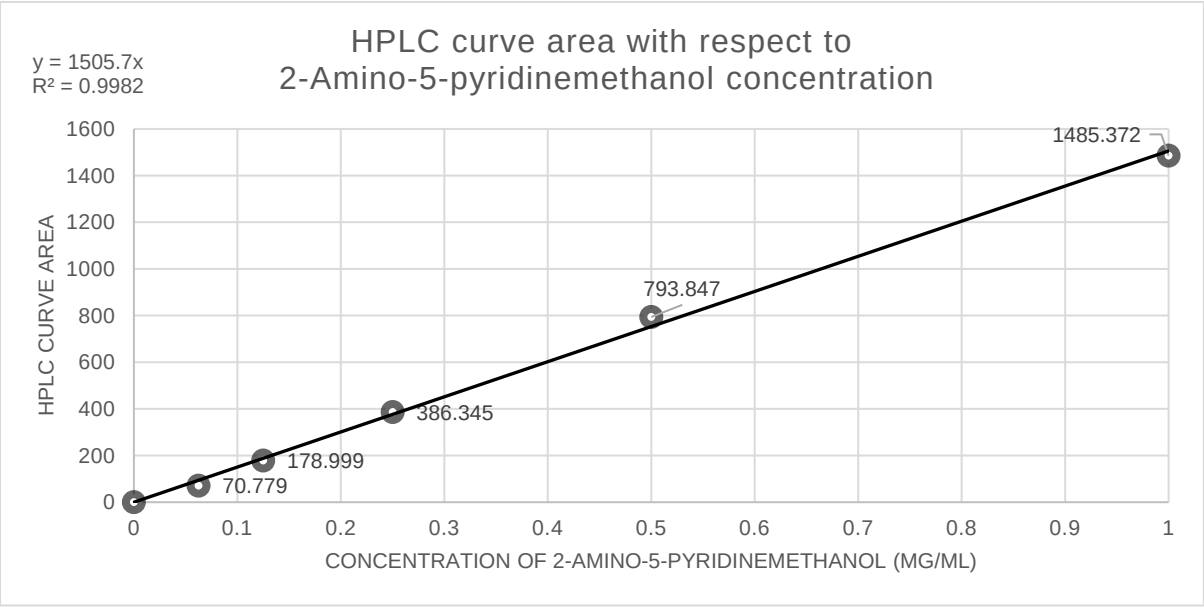
3-Methyl-2-aminopyridine 1b



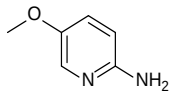


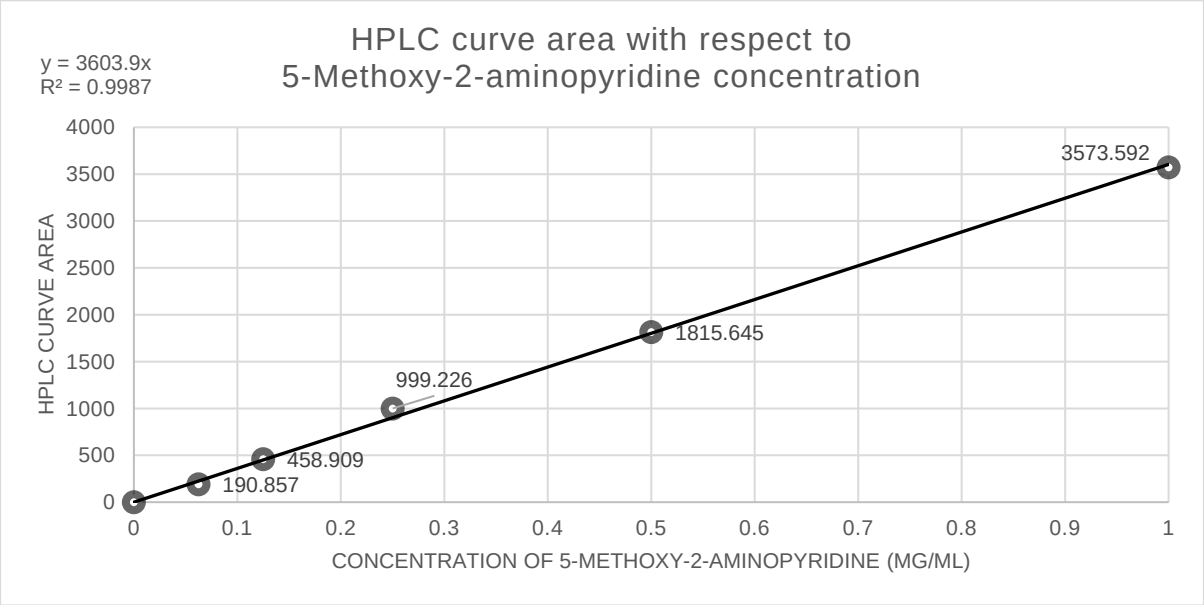
(6-Aminopyridin-3-yl)methanol 1c



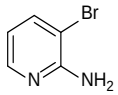


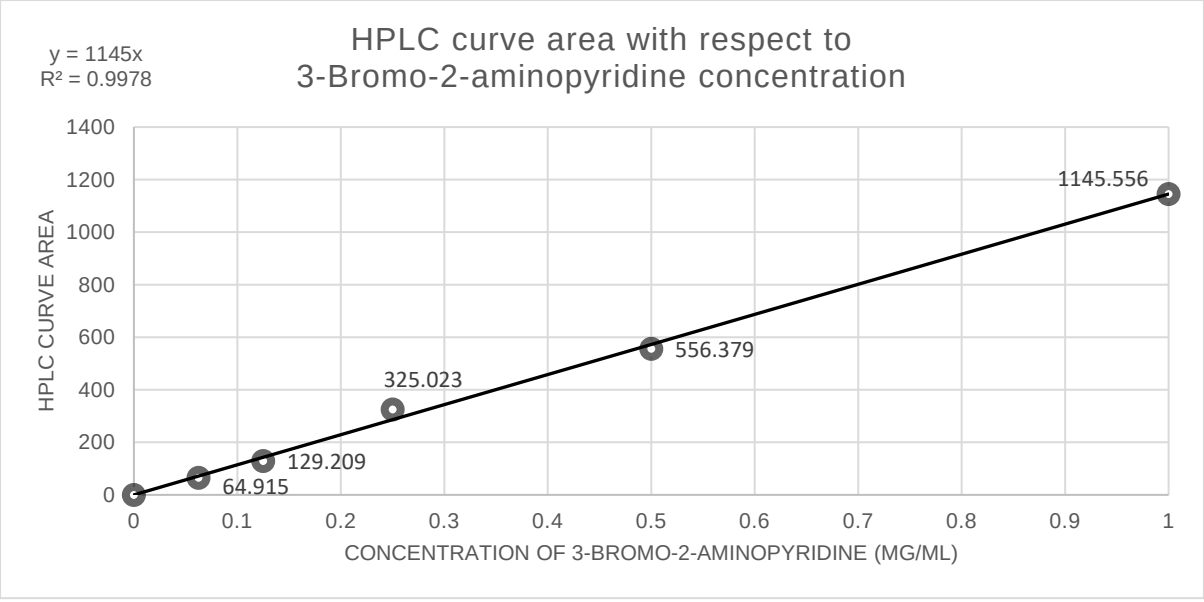
5-Methoxy-2-aminopyridine 1d



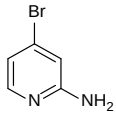


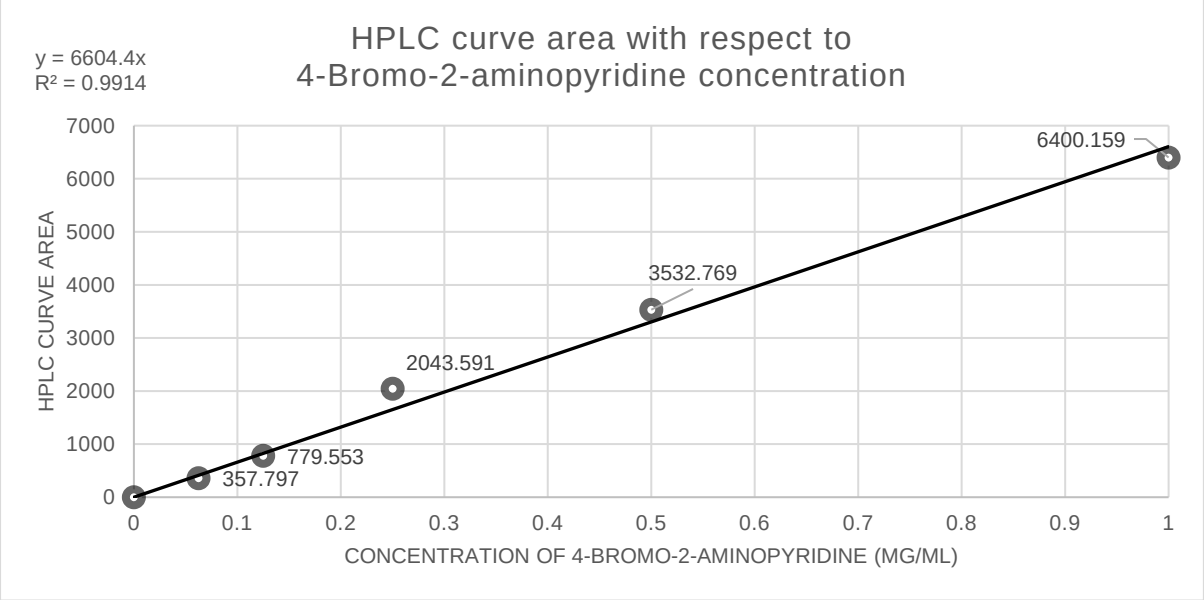
3-Bromo-2-aminopyridine 1e



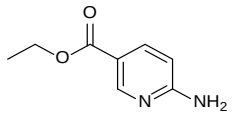


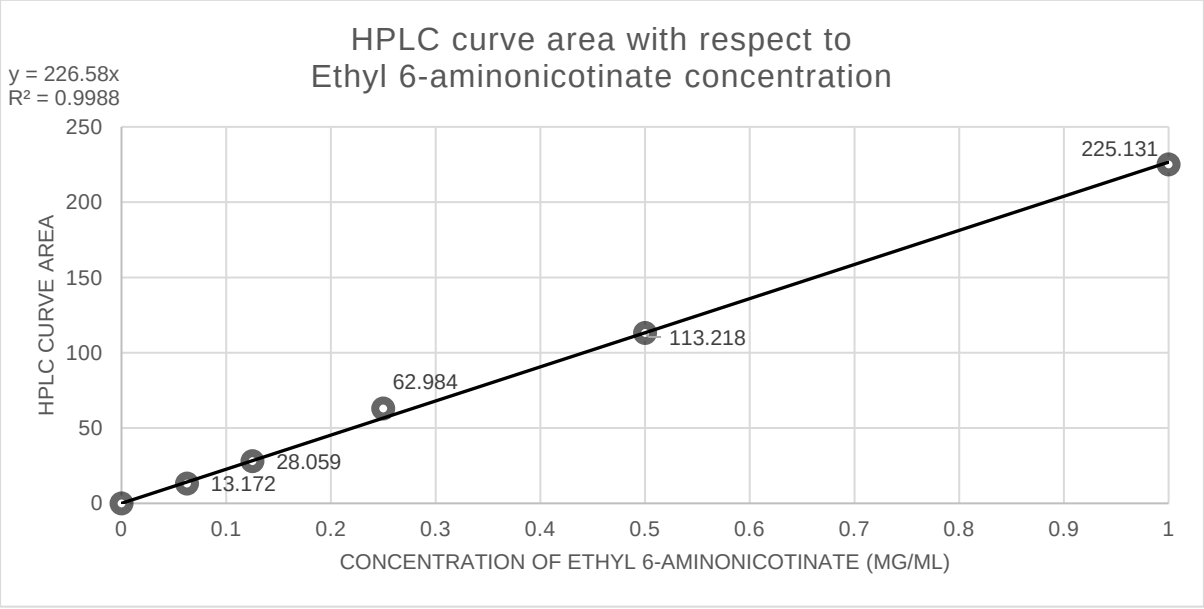
4-Bromo-2-aminopyridine 1f



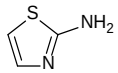


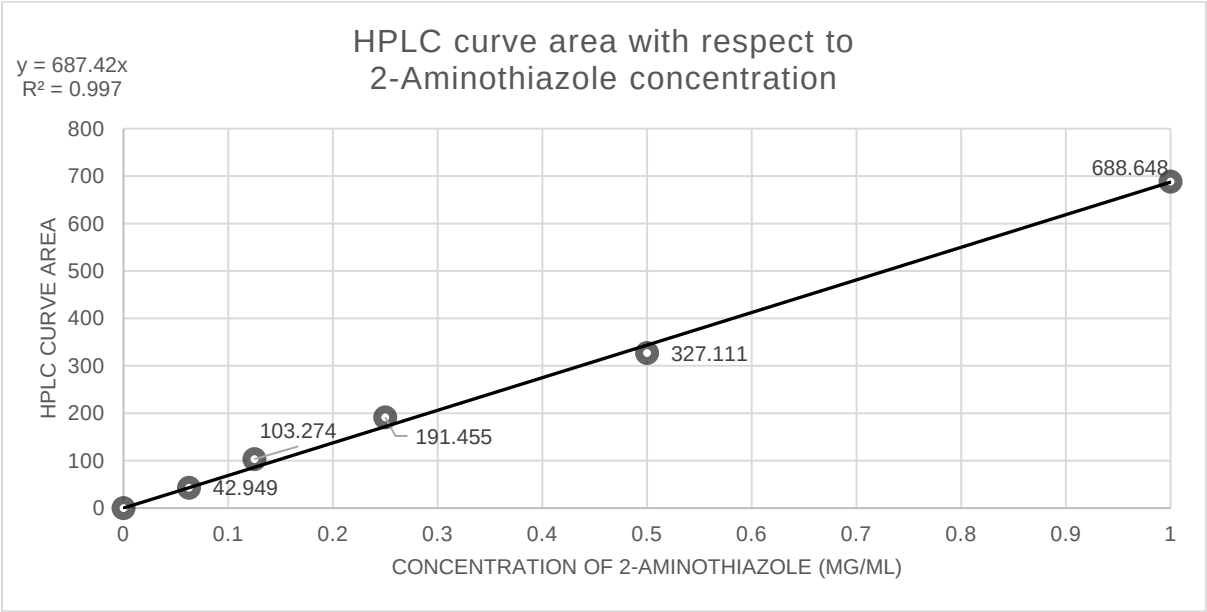
Ethyl 6-aminonicotinate 1g



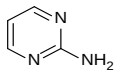


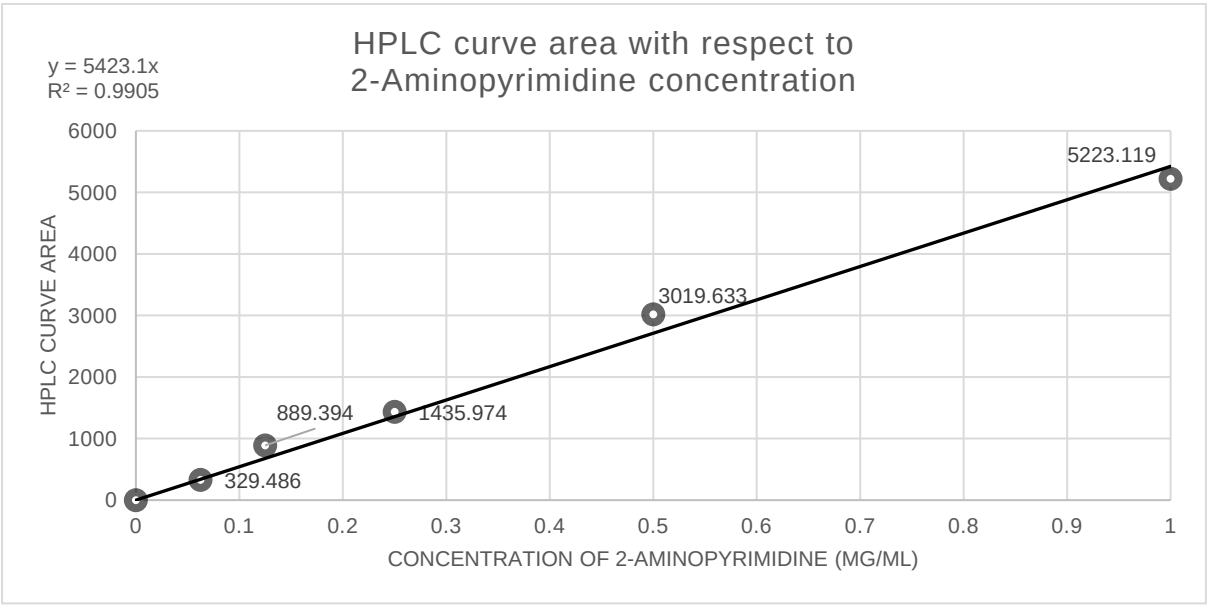
2-Aminothiazole 1h



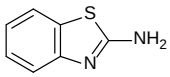


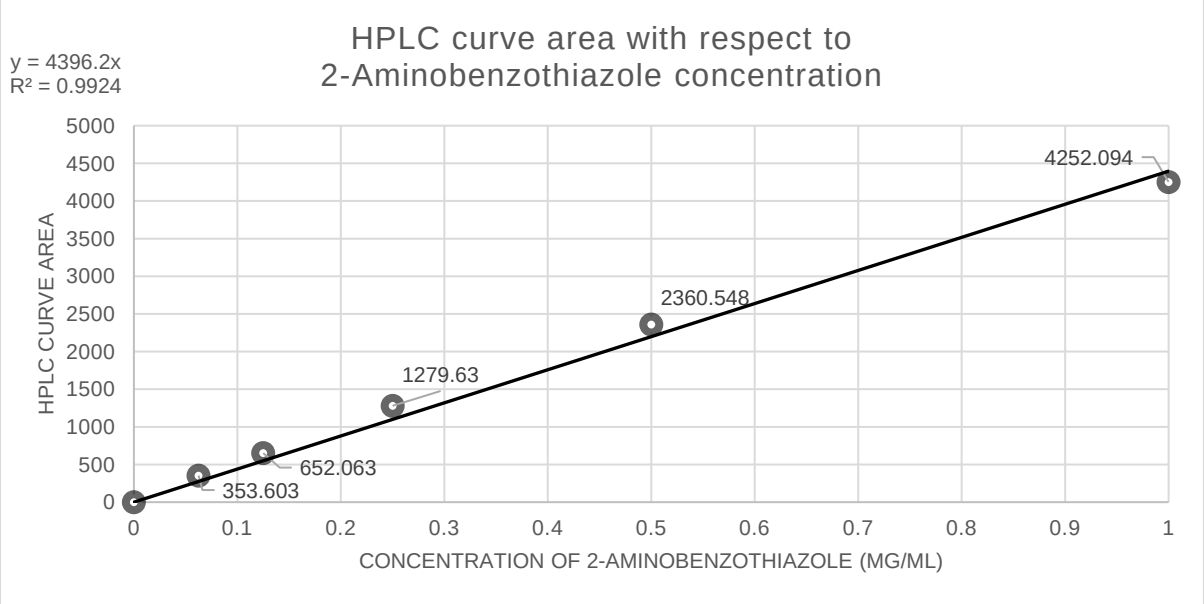
2-Aminopyrimidine 1i



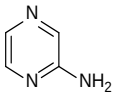


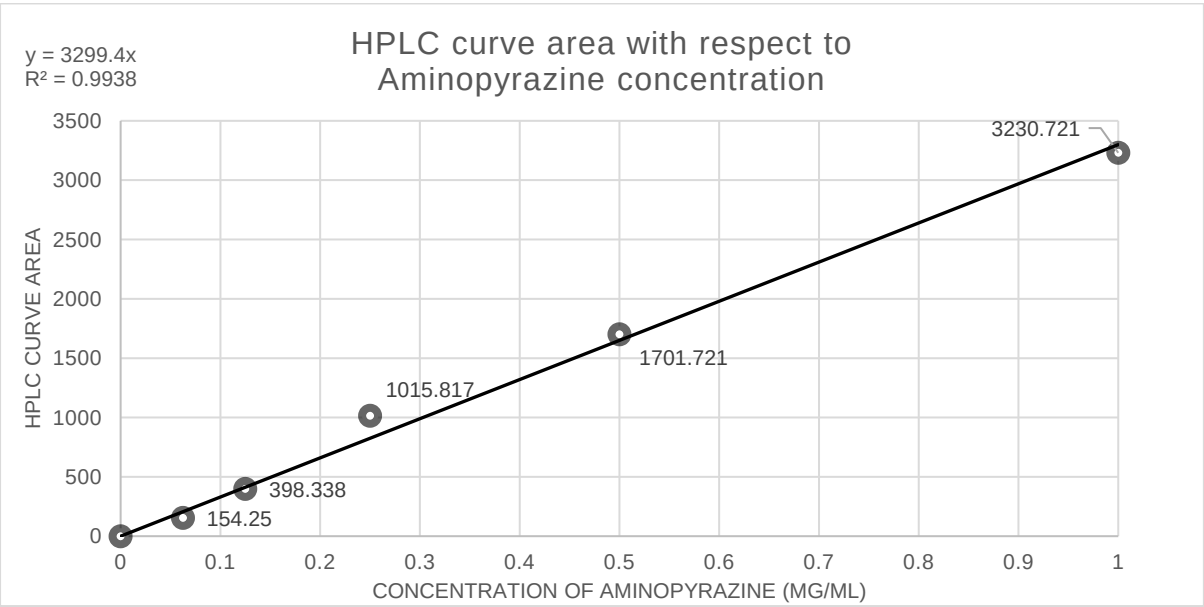
2-Aminobenzothiazole 1j



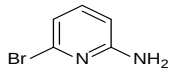


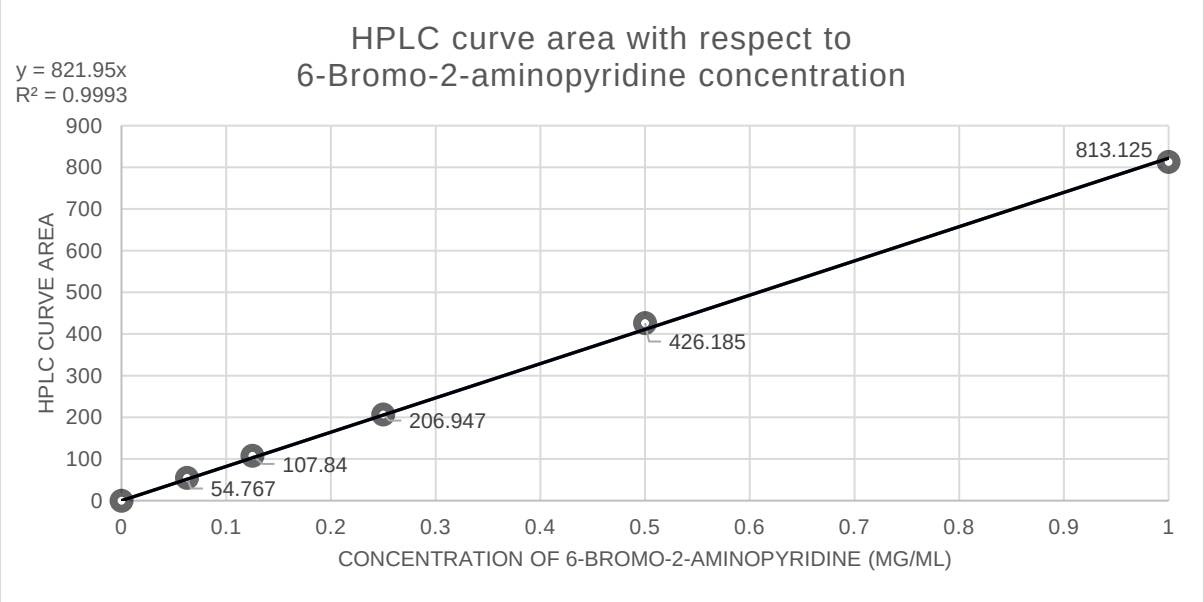
Aminopyrazine 1k



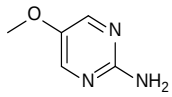


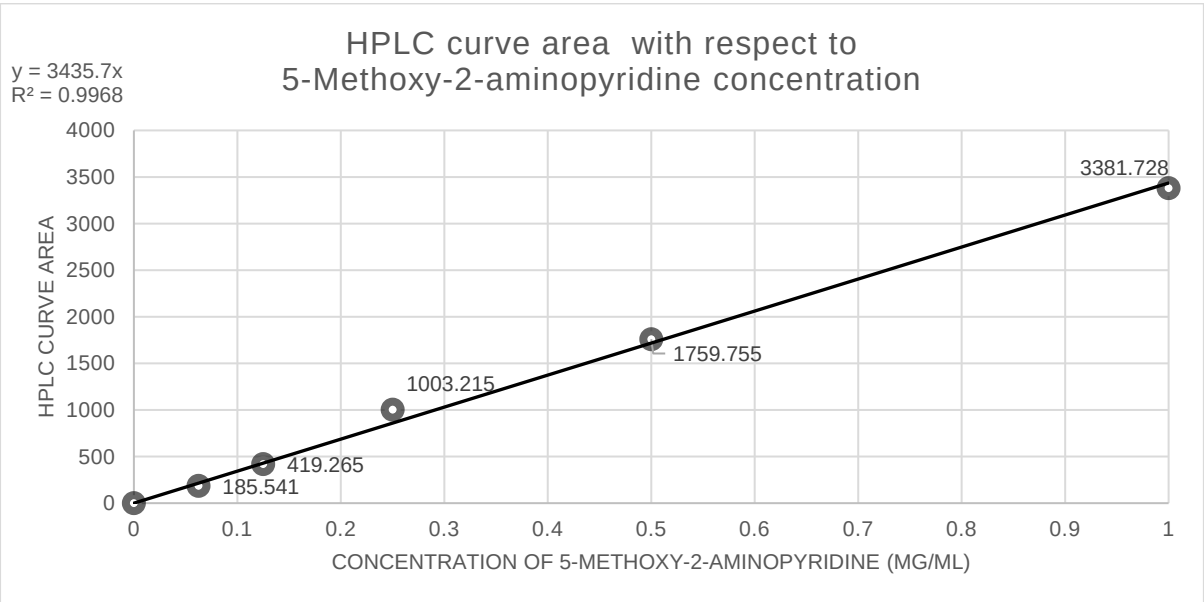
6-Bromo-2-aminopyridine 1l





5-Methoxy-2-aminopyrimidine 1m





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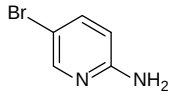
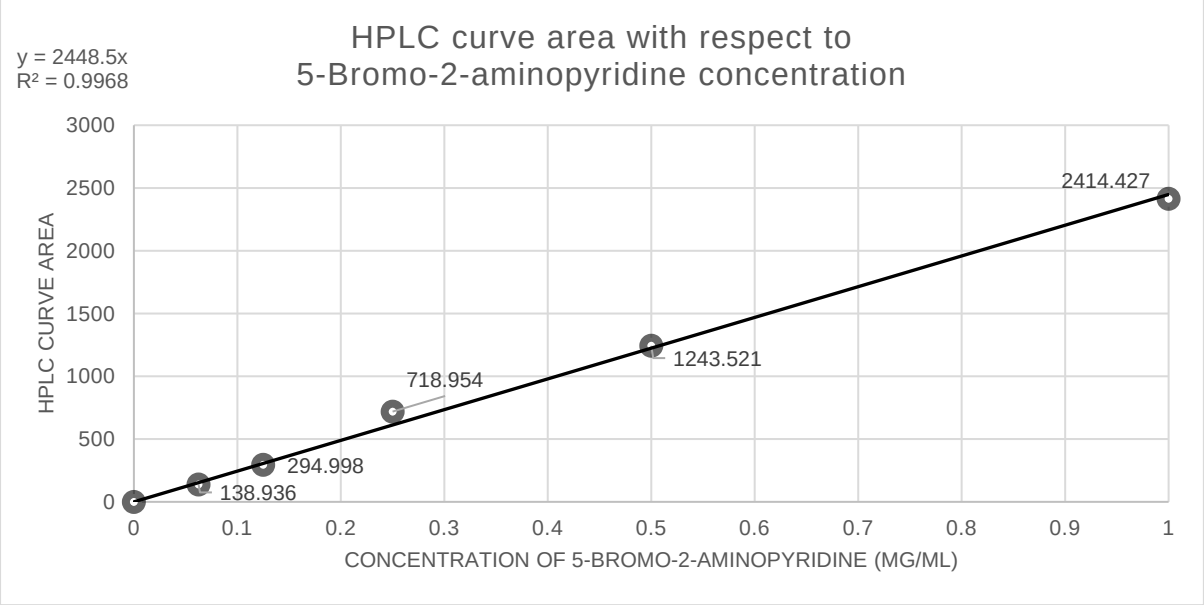




4.1. Procedure for deriving conversion estimates from HPLC concentration gradients

Following flow reaction procedures, X µL (see section **5. Synthetic Procedures**) was removed from the crude reaction mixture and diluted with 1 mL methanol. The solution was analysed by HPLC. The area under curve (AUC) data from the HPLC run was attained, and, using the relevant concentration gradient, calculated as a concentration of starting material (in mg/(1.00 mL + X µL)) remaining in the crude reaction mixture. As the crude reaction mixture tested was present as a solution of (1.00 mL + X µL) total volume, the value was adjusted (divided by (1.00 + X)) to provide the data as a concentration in mg/mL.

Subsequently, taking the calculated concentration value of the crude material as a proportion of the maximal starting material concentration remaining in the reaction (if no starting material had been consumed) allowed for the calculation of remaining starting material in the reaction composition. As such, the equation used to calculate HPLC conversion is:

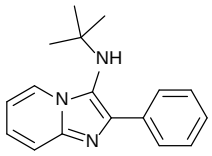
$$SM\ Consumption = \left(1 - \frac{(Concentration\ of\ SM\ left\ in\ mixture\ (from\ AUC) \div (1.00 + X)\ )}{\begin{array}{c}Maximal\ SM\ concentration\ in \\ x\ \mu L\ reaction\ volume (conditions\ if\ no\ consumption\ was\ observed)\end{array}}\right) \times 100$$

Equation S1: Calculation of starting material consumption in the reaction by HPLC analysis.

5. Synthetic procedures

5.1. General Synthetic Procedures

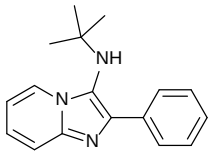
General procedure A: Optimisation of the synthesis of *N*-(*tert*-butyl)-2-phenylimidazo [1,2-a]pyridin-3-amine 4a, thermal conditions (Manuscript Table 1, Entries 1-4)



4a

In a 5 mL reaction tube was prepared a solution of 2-aminopyridine **1a** (100 mg, 1.06 mmol) and benzaldehyde **2a** (0.108 mL, 1.06 mmol) in 3 mL of the chosen solvent described in entries 1-4, **Manuscript Table 1**. 10 mol% (0.106 mmol) of the relevant catalyst was added to each reaction, before *N*-*tert*-butylisocyanide **3a** (0.120 mL, 1.06 mmol) was added to each, and the reaction mixtures were then heated to 50 °C for 24 h. The reactions were sampled (20 µL taken) and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients) at time points of 1 h, 2 h and 20 h. After 24 h, the final aliquot was removed and analysed by HPLC analysis by the same method to determine the end point conversion. The products were not isolated.

General procedure B: Optimisation of the synthesis of *N*-(*tert*-butyl)-2-phenylimidazo [1,2-a]pyridin-3-amine 4a, microwave conditions (Manuscript Table 1, Entries 6-9)



4a

To a 5 mL microwave vial was added a solution of 2-aminopyridine **1a** (100 mg, 1.06 mmol), benzaldehyde **2a** (either **(a)** 108 µL, 1.06 mmol or **(b)** 216 µL, 2.13 mmol), *N*-*tert*-butylisocyanide **3a** (either **(c)** 120 µL, 1.06 mmol or **(d)** 240 µL, 2.13 mmol) and one of: 4 M HCl (solution in dioxane, either **(e)** 266 µL, 1.06 mmol or **(f)** 27.0 µL, 0.106 mmol), 1.25 M HCl (solution in ethanol, **(g)** 85.0 µL, 0.106 mmol), or no catalyst **(h)** was added in ethanol solvent (3 mL). The reaction mixture was irradiated at 130 °C for 50 min, before an aliquot (of either **(i)** 5 µL or **(j)** 10 µL) was taken, and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients) to determine starting material consumption. In all cases, the products were not isolated.

General procedure C: Flow GBBR method using aryl- and heteroaryl aldehydes, giving products 4a-4q (Manuscript Table 1, Entry 10, and Scheme 4)

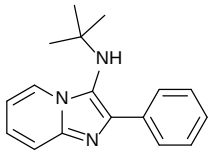
A stock solution of the aminoazine (2.00 mmol), aryl or heteroaryl aldehyde (4.00 mmol or 2.00 mmol), and HCl solution (1.25 M in ethanol, 0.160 mL, 0.200 mmol) was prepared in ethanol (10 mL total solution volume). Then, a solution of the relevant isocyanide (4.00 mmol) was prepared in ethanol (10 mL total solution volume). The flow reactor was heated to 130 °C whilst pumping clean ethanol through the system at a flow rate of 0.1 mL/min/line. Once at temperature, each of the two input lines was placed into one of the two stock solutions, and the reagents were pumped at 0.1 mL/min/line for 50 min (5 mL removed from each solution). The input lines were then changed back to the solvent reservoir and pumped to waste for 25 min to account for the dead volume in the reactor. The product solution was then collected for 61.75 min (12.4 mL collected), after which time the flow reactor was cooled and turned off. The reaction solutions were then analysed by the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients) to determine starting material consumption. The remaining crude material was isolated by either passage through an Isolute® 5 g aminopropyl frit followed by drying *in vacuo*, or concentrated directly *in vacuo*, and, if required, purified by flash column chromatography.

General procedure D: Flow GBBR method using alkyl aldehydes, giving products 4r-4t, 4v-4z (Manuscript Scheme 5)

A stock solution of the aminoazine (2.00 mmol), and isocyanide (4.00 mmol) was prepared in ethanol (10 mL total solution volume). Then, a solution of the formaldehyde (2.24 mmol), or alkyl aldehyde (4.00 mmol), and 1.25 M HCl (solution in ethanol, 0.160 mL, 0.200 mmol) was prepared in ethanol (10 mL total solution volume). The flow reactor was heated to 130 °C whilst pumping clean ethanol through the system at a flow rate of 0.1 mL/min/line. Once at temperature, each of the two input lines was placed into one of the two stock solutions, and the reagents were pumped at 0.1 mL/min/line for 50 min (5 mL removed from each solution). The input lines were changed back to the solvent reservoir and pumped to waste for 25 min to account for the dead volume in the reactor. The desired product solution was then collected for 61.75 min (12.4 mL collected), after which time the flow reactor was cooled and turned off. The reaction solutions were then analysed by the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients) to determine starting material consumption. The product was isolated by concentration *in vacuo*, and, if required, purified by flash column chromatography.

5.2. Reaction Optimisation

Optimisation of the synthesis of *N*-(*tert*-butyl)-2-phenylimidazo [1,2-a]pyridin-3-amine 4a, under thermal conditions (Manuscript Table 1, Entries 1-4)



4a

Following General Procedure A, the data are given below as (a) solvent; (b) catalyst; (c) HPLC conversion after 24 h; and (d) any further observations.

Table 1, Entry 1: (a) toluene solvent; (b) $Sc(OTf)_3$ (52.3 mg, 0.106 mmol); (c) quantitative conversion; (d) heterogenous mixture.

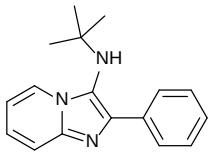
Table 1, Entry 2: (a) methanol solvent; (b) $HClO_4$ (70 % wt. in H_2O, 9.2 µL, 0.106 mmol); (c) 92 % conversion.

Table 1, Entry 3: (a) acetonitrile solvent; (b) HCl (4 M solution in dioxane, 27 µL, 0.106 mmol); (c) 77 % conversion.

Table 1, Entry 4: (a) ethanol solvent; (b) HCl (4 M solution in dioxane, 27 µL, 0.106 mmol); (c) 91 % conversion.

See Section 5.3 for analytical data for compound **4a**.

Optimisation of the synthesis of *N*-(*tert*-butyl)-2-phenylimidazo [1,2-a]pyridin-3-amine 4a, under microwave conditions (Manuscript Table 1, Entries 6-9)



4a

Following General Procedure B, the reaction conditions are shown below, with the accompanying level of conversion as determined by HPLC analysis.

Table 1, Entry 6: Conditions used: **(a)**, **(c)**, **(e)**, **(i)**, 75 % conversion.

Table 1, Entry 7: Conditions used: **(a)**, **(c)**, **(h)**, **(i)**, 36 % conversion.

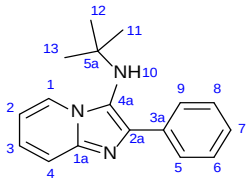
Table 1, Entry 8: Conditions used: **(b)**, **(d)**, **(f)**, **(j)**, quantitative conversion.

Table 1, Entry 9: Conditions used: **(b)**, **(d)**, **(g)**, **(j)**, quantitative conversion.

See the following section, Section 5.3, for compound data, and for the experiments relating to **Manuscript Table 1, Entries 5 and 10**.

5.3. Synthetic Procedures

N-(*tert*-Butyl)-2-phenylimidazo[1,2-a]pyridin-3-amine 4a



4a

Preparation under MW conditions (Table 1, Entry 5): To a 5 mL microwave vial was added a solution of 2-aminopyridine **1a** (0.100 g, 1.06 mmol), benzaldehyde **2a** (0.108 mL, 1.06 mmol), *N*-*tert*-butylisocyanide **3a** (0.120 mL, 1.06 mmol) and HCl (4 M solution in dioxane 27 μL, 0.106 mmol) in ethanol (3 mL). The reaction mixture was irradiated at 130 °C for 50 min. After cooling, a 10 μL aliquot was removed from the reaction mixture and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 93 % of the starting material had been consumed in the reaction. The remaining reaction mixture was dried *in vacuo*, and the residue purified by flash column chromatography using a 40 g RediSep silica cartridge, with an elution gradient of cyclohexane to 40 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford *N*-(*tert*-butyl)-2-phenylimidazo[1,2-a]pyridin-3-amine **4a** (236 mg, 0.889 mmol, 84 % yield) as an off-white solid.

Preparation under flow conditions (Table 1, Entry 10)

The reaction was performed according to **General Procedure C**, using 2-aminopyridine **1a** (94.0 mg, 1.00 mmol,), benzaldehyde **2a** (0.203 mL, 2.00 mmol) and *N*-*tert*-butylisocyanide **3a** (0.226 mL, 2.00 mmol) as the reaction components. Following the reaction, a 50 μL aliquot was removed from the reaction mixture, diluted with 0.95 mL methanol, and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 97% of the starting material had been consumed in the reaction. The crude reaction mixture was passed through an Isolute® 5 g aminopropyl frit, washing with 20 mL methanol, before solvent removal *in vacuo* afforded *N*-(*tert*-butyl)-2-phenylimidazo[1,2-a]pyridin-3-amine **4a** (256 mg, 0.965 mmol, 96 % yield) as an off-white/yellow solid.

mp: 166-167 °C.

IR ν_{max} (cm^{-1}): 3319, 2968, 1443, 1362, 1331, 1209, 757, 701.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (app. dt, *J* = 7.1, $^4J_{HH}$ = 1.3 Hz, 1H, CH^1), 7.90 (m, 2H, CH^5 + CH^9), 7.53 (app. dt, *J* = 9.1, $^4J_{HH}$ = 1.0 Hz, 1H, CH^4), 7.45 - 7.40 (m, 2H, CH^6 + CH^8), 7.32 (tt, *J* = 7.6,

$^4J_{HH}$ = 1.3 Hz, 1H, CH^7), 7.12 (ddd, *J* = 9.1, 7.1, $^4J_{HH}$ = 1.0 Hz, 1H, CH^3), 6.76 (td, *J* = 6.8, $^4J_{HH}$ = 1.0 Hz, 1H, CH^2), 3.10 (br. s, 1H, NH^{10}), 1.04 (s, 9H, $CH_3{}^{11}$, $CH_3{}^{12}$ + $CH_3{}^{13}$).

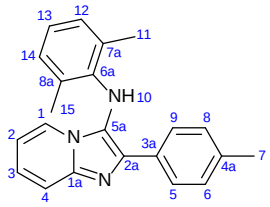
^{13}C NMR (101 MHz, $CDCl_3$): δ 142.1 (C^{1a}), 139.6 (C^{4a}), 135.4 (C^{3a}), 128.3 (C^6H + C^8H), 128.2 (C^5H + C^9H), 127.3 (C^7H), 123.9 (C^3H), 123.5 (C^{2a} + C^1H), 117.4 (C^4H), 111.2 (C^2H), 56.4 (C^{5a}), 30.3 ($C^{11}H_3$, $C^{12}H_3$ + $C^{13}H_3$).

The spectroscopic data is in accordance with that reported in the literature.[2]

LCMS (High pH, UV, ESI): R_t = 1.16 min, $[M+H]^+$ m/z = 266.2.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{17}H_{20}N_3$: 266.1657; found: 266.1667.

***N*-(2,6-Dimethylphenyl)-2-(p-tolyl)imidazo[1,2-a]pyridin-3-amine 4b**



4b

The reaction was performed according to **General Procedure C**, using 2-aminopyridine **1a** (94.0 mg, 1.00 mmol), 4-methylbenzaldehyde **2b** (0.236 mL, 2.00 mmol) and 2,6-dimethylphenylisocyanide (262 mg, 2.00 mmol) **3b** as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 83% of the starting material had been consumed in the reaction. The crude mixture was passed through an Isolute® 5 g aminopropyl frit, washing with 20 mL methanol, before solvent removal *in vacuo* afforded the crude product, which was purified by flash column chromatography using a 40 g RediSep silica cartridge, with an elution gradient of cyclohexane to 30 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and solvent removed *in vacuo* to afford *N*-(2,6-dimethylphenyl)-2-(p-tolyl)imidazo[1,2-a]pyridin-3-amine **4b** (267 mg, 0.815 mmol, 82 % yield) as an off-white solid.

mp: 189-190 °C (dec.)

IR ν_{max} (cm^{-1}): 3364, 1562, 1470, 1231, 825, 747.

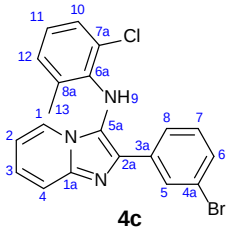
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (br. d, *J* = 8.1 Hz, 2H, CH^5 + CH^9), 7.58-7.53 (m, 2H, CH^1 + CH^4), 7.16 (d, *J* = 8.1 Hz, 2H, CH^6 + CH^8), 7.11 (ddd, *J* = 9.1, 6.5, $^4J_{HH}$ = 1.0 Hz, 1H, CH^3), 6.96 (d, *J* = 7.6 Hz, 2H, CH^{12} + CH^{14}), 6.78 (t, *J* = 7.6 Hz, 1H, CH^{13}), 6.65 (td, *J* = 6.5, $^4J_{HH}$ = 1.0 Hz, 1H, CH^2), 5.37 (br. s, 1H, NH^{10}), 2.35 (s, 3H, $CH_3{}^7$), 2.00 (s, 6H, $CH_3{}^{11}$ + CH^{15}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.3 (C^{1a}), 140.3 (C^{5a}), 139.4 (C^{6a}), 137.4 (C^{2a}), 129.9 ($C^{12}H$ + $C^{14}H$), 129.2 ($C^{6}H$ + $C^{8}H$), 127.0 ($C^{5}H$ + $C^{9}H$), 125.3 (C^{7a} + C^{8a}), 124.1 ($C^{3}H$), 122.2 ($C^{1}H$), 121.0 ($C^{13}H$), 120.4 (C^{3a}), 119.6 (C^{4a}), 117.5 ($C^{4}H$), 112.2 ($C^{2}H$), 21.3 ($C^{7}H_3$), 18.5 ($C^{11}H_3$ + $C^{15}H_3$).

LCMS (High pH, UV, ESI): R_t = 1.30 min, $[M+H]^+$ m/z 328.1.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{22}H_{22}N_3$: 328.1808, found: 328.1798.

2-(3-Bromophenyl)-*N*-(2-chloro-6-methylphenyl)imidazo[1,2-a]pyridin-3-amine 4c



4c

The reaction was performed according to **General Procedure C**, using 2-aminopyridine **1a** (94.0 mg, 1.00 mmol), 3-bromobenzaldehyde **2c** (0.233 mL, 2.00 mmol) and 2-chloro-6-methylphenylisocyanide **3c** (303 mg, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 88% of the starting material had been consumed in the reaction. The crude mixture was passed through an Isolute® 5 g aminopropyl frit, washing with 30 mL methanol, before solvent removal *in vacuo* afforded the crude product, which was purified by flash column chromatography using a 40 g RediSep silica cartridge, with an elution gradient of cyclohexane to 30 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and solvent removed *in vacuo* to afford 2-(3-bromophenyl)-*N*-(2-chloro-6-methylphenyl)imidazo[1,2-a]pyridin-3-amine **4c** (345 mg, 0.836 mmol, 84 % yield) as a white powder.

mp: 188-189 °C (dec.)

IR ν_{max} (cm^{-1}): 3309, 1596, 1466, 1351, 753, 681.

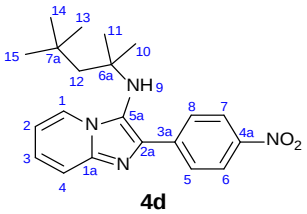
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (app. t, *J* = 1.5 Hz, 1H, CH^{1}), 7.96 (dt, *J* = 7.6, $^{4}J_{HH}$ = 1.5 Hz, 1H, CH^{8}), 7.86 (dt, *J* = 6.6, $^{4}J_{HH}$ = 1.0 Hz, 1H, CH^{6}), 7.62 (br. d, *J* = 9.1 Hz, 1H, CH^{4}), 7.36 (ddd, *J* = 8.1, 2.0, $^{5}J_{HH}$ =1.0 Hz, 1H, CH^{7}), 7.28 (dd, *J* = 8.1, $^{4}J_{HH}$ = 1.5 Hz, 1H, CH^{3}), 7.24-7.17 (m, 2H, CH^{10} + CH^{12}), 6.85 (d, *J* = 7.1 Hz, 1H, CH^{5}), 6.81 (td, *J* = 6.6, $^{4}J_{HH}$ = 1.0 Hz, 1H, CH^{2}), 6.77 (t, *J* = 7.6 Hz, 1H, CH^{11}), 6.12 (br. s, 1H, NH^{9}), 1.56 (s, 3H, $CH_3{}^{13}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.7 (C^{1a}), 138.5 (C^{6a}), 136.9 (C^{5a}), 135.1 (C^{3a}), 131.2 ($C^{5}H$), 130.6 ($C^{7}H$), 130.1 ($C^{1}H$), 129.8 ($C^{12}H$), 127.6 ($C^{3}H$), 127.5 (C^{2a}), 125.7 ($C^{8}H$), 125.1 ($C^{10}H$), 123.1 (C^{8a}), 122.6 (C^{7a}), 122.5 ($C^{6}H$), 121.7 ($C^{11}H$), 120.0 (C^{4a}), 117.7 ($C^{4}H$), 112.8 ($C^{2}H$), 18.2 ($C^{13}H_3$).

LCMS (High pH, UV, ESI): R_t = 1.35 min, $[M+H]^+$ m/z 412.0.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{20}H_{16}{}^{79}Br^{35}ClN_3$: 412.0216, found: 412.0206. m/z calculated for $[M+H]^+$ $C_{20}H_{16}{}^{79}Br^{37}ClN_3$: 414.0187; m/z calculated for $[M+H]^+$ $C_{20}H_{16}{}^{81}Br^{35}ClN_3$: 414.0196; found: 414.0181. m/z calculated for $[M+H]^+$ $C_{20}H_{16}{}^{81}Br^{37}ClN_3$: 416.0166, found: 416.0163.

2-(4-Nitrophenyl)-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-a]pyridin-3-amine 4d



4d

The reaction was performed according to **General Procedure C**, using 2-aminopyridine **1a** (94.0 mg, 1.00 mmol), 4-nitrobenzaldehyde **2d** (302 mg, 2.00 mmol) and 1,1,3,3-tetramethylbutylisocyanide **3d** (351 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 91% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the resulting crude product was purified by flash column chromatography using a 40 g RediSep silica cartridge, with an elution gradient of 10 % ethyl acetate in cyclohexane to 40 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford 2-(4-nitrophenyl)-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-a] pyridin-3-amine **4d** (267 mg, 0.729 mmol, 73 % yield) as a bright orange powder.

An analytically pure sample was prepared *via* MDAP isolation (High pH), Method D, 30 min run.

mp: 159-160 °C

IR ν_{max} (cm^{-1}): 2946, 1588, 1497, 1330, 752.

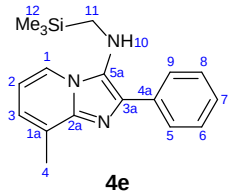
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31-8.27 (m, 2H, CH^6 + CH^7), 8.22-8.17 (m, 3H, CH^1, CH^5 + CH^8), 7.55 (app. dt, *J* = 8.9, $^4J_{HH}$ = 1.0 Hz, 1H, CH^4), 7.19 (ddd, *J* = 8.8, 6.9, $^4J_{HH}$ = 1.5 Hz, 1H, CH^3), 6.83 (td, *J* = 6.4, $^4J_{HH}$ = 1.5 Hz, 1H, CH^2), 3.13 (br. s, 1H, NH^9), 1.64 (2H, s, $CH_2{}^{12}$), 1.07 (9H, s, $CH_3{}^{13}$, $CH_3{}^{14}$ + $CH_3{}^{15}$), 1.00 (6H, s, $CH_3{}^{10}$ + $CH_3{}^{11}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.8 (C^{4a}), 142.6 (C^{1a}), 142.3 (C^{3a}), 137.5 (C^{5a}), 128.7 (C^1H), 124.9 (C^3H), 124.6 (C^{2a}), 123.6 (C^6H + C^7H), 123.5 (C^5H + C^8H), 117.8 (C^4H), 112.0 (C^2H), 61.1 (C^{6a}), 57.3 ($C^{12}H_2$), 31.9 ($C^{13}H_3$,$C^{14}H_3$ + $C^{15}H_3$), 31.8 (C^{7a}), 29.2 ($C^{10}H_3$ + $C^{11}H_3$).

LCMS (High pH, UV, ESI): R_t = 1.44 min, $[M+H]^+$ m/z 367.2.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{21}H_{27}N_4O_2$: 367.2129, found: 367.2118.

8-Methyl-*N*-((trimethylsilyl)methyl)imidazo[1,2-a]pyridin-3-amine 4e



4e

The reaction was performed according to **General Procedure C**, using 3-methyl-2-aminopyridine **1b** (101 µL, 1.00 mmol), benzaldehyde **2a** (203 µL, 2.00 mmol) and (isocyanomethyl)trimethylsilane **3e** (282 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 64% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, then the crude residue was purified by flash column chromatography using an 80 g RediSep silica cartridge, with an elution gradient of cyclohexane to 10 % TBME in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford 8-methyl-*N*-((trimethylsilyl)methyl)imidazo[1,2-a]pyridin-3-amine **4e** (169 mg, 0.546 mmol, 55 % yield) as a white crystalline solid.

Analytically pure sample prepared *via* MDAP isolation (High pH), Method D, 30 min run.

mp: 80-81 °C

IR ν_{max} (cm^{-1}): 2952, 1494, 1349, 1246, 844.

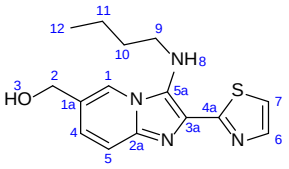
^{1}H NMR (400 MHz, CD_3Cl): δ 7.99-7.94 (m, 2H, CH^5 + CH^9), 7.86 (d, *J* = 6.9 Hz, 1H, CH^1), 7.48-7.43 (m, 2H, CH^6 + CH^8), 7.31 (tt, *J* = 7.4 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, CH^7), 6.92 (app. dt, *J* = 6.8, $^4J_{HH}$ = 1.1 Hz, 1H, CH^3), 6.71 (t, *J* = 6.9 Hz, 1H, CH^2), 2.92 (br. s, 1H, NH^{10}), 2.64 (s, 3H, $CH_3{}^4$), 2.56 (s, 2H, $CH_2{}^{11}$), 0.16 (s, 9H, $CH_3{}^{12}$, $CH_3{}^{13}$ + $CH_3{}^{14}$).

^{13}C NMR (101 MHz, CD_3Cl): δ 141.6 (C^{2a}), 134.7 (C^{5a}), 134.3 (C^{4a}), 129.1 (C^{3a}), 128.6 (C^6H + C^8H), 127.4 (C^{1a}), 127.1 (C^5H, C^7H + C^9H), 122.4 (C^3H), 120.1 (C^1H), 111.6 (C^2H), 38.6 ($C^{11}H_2$), 16.7 (C^4H_3), -2.78 ($C^{12}H_3$, $C^{13}H_3$ + $C^{14}H_3$).

LCMS (High pH, UV, ESI): R_t = 1.41 min, $[M+H]^+$ m/z 310.2.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{18}H_{24}N_3Si$: 310.1739, found: 310.1740.

(3-(Butylamino)-2-(thiazol-2-yl)imidazo[1,2-a]pyridin-6-yl)methanol 4f



4f

The reaction was performed according to **General Procedure C**, using (6-aminopyridin-3-yl)methanol **1c** (124 mg, 1.00 mmol), thiazole-2-carbaldehyde **2e** (88 µL, 1.00 mmol) and 1-isocyanobutane **3f** (209 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 78% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by reverse phase flash column chromatography using a 60 g Biotage SNAP KPC18-HS cartridge, with an elution gradient from 5 % acetonitrile and 95 % 10 mM aqueous ammonium bicarbonate solution (adjusted to pH10 with 0.88 M aqueous ammonia) to 50 % acetonitrile. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford (3-(butylamino)-2-(thiazol-2-yl)imidazo[1,2-a]pyridin-6-yl)methanol **4f** (154 mg, 0.509 mmol, 51 % yield) as a viscous yellow oil.

IR ν_{max} (cm^{-1}): 3159, 2845, 2371, 1575, 1268, 1059, 787.

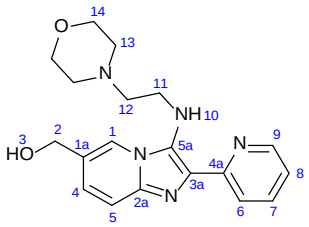
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.89 (m, 1H, CH^{1}), 7.83 (d, *J* = 3.4 Hz, 1H, CH^{6}), 7.41 (d, *J* = 9.3 Hz, 1H, CH^{5}), 7.28 (d, *J* = 3.4 Hz, 1H, CH^{7}), 7.06 (dd, *J* = 9.3, $^{4}J_{HH}$ = 1.5 Hz, 1H, CH^{4}), 5.34 (br. s, 1H, NH^{8}), 4.66 (d, *J* = 1.0 Hz, 2H, CH_2^{2}), 3.10 (t, *J* = 7.3 Hz, 2H, CH_2^{9}), 2.91 (br. s, 1H, OH^{3}), 1.62-1.54 (m, 2H, CH_2^{10}), 1.42 (sxt, *J* = 7.4 Hz, 2H, CH_2^{11}), 0.90 (t, *J* = 7.4 Hz, 3H, CH_3^{12}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.9 (C^{4a}), 143.2 ($C^{6}H$), 140.4 (C^{2a}), 131.1 (C^{5a}), 126.2 ($C^{4}H$), 126.0 (C^{3a}), 124.8 ($C^{1}H$), 120.4 (C^{1a}), 117.6 ($C^{7}H$), 117.3 ($C^{5}H$), 62.5 ($C^{2}H_2$), 47.0 ($C^{9}H_2$), 32.6 ($C^{10}H_2$), 20.1 ($C^{11}H_2$), 13.8 ($C^{12}H_3$).

LCMS (High pH, UV, ESI): R_t = 0.96 min, $[M+H]^+$ m/z 303.2.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{15}H_{19}N_4OS$: 303.1280, found: 303.1279.

(3-((2-Morpholinoethyl)amino)-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-6-yl)methanol 4g



4g

The reaction was performed according to **General Procedure C**, using (6-aminopyridin-3-yl)methanol **1c** (124 mg, 1.00 mmol), picolinaldehyde **2f** (190 µL, 2.00 mmol) and 4-(2-isocyanoethyl)morpholine (276 µL, 2.00 mmol) **3g** as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 92% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography using an 80 g Biotage RediSep silica cartridge, with an elution gradient of 5 % ethyl acetate in cyclohexane to 30 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford (3-((2-morpholinoethyl)amino)-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-6-yl) methanol **4g** (309 mg, 0.874 mmol, 87 % yield) as a beige powder.

mp: 143-144 °C

IR ν_{max} (cm^{-1}): 3164, 2803, 1896, 1113, 1018, 793.

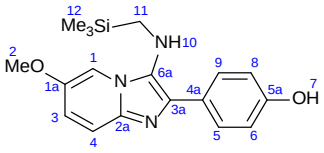
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.52 (m, 1H, CH^9), 8.14 (br. d, *J* = 7.9 Hz, 1H, CH^1), 7.97-7.93 (m, 1H, CH^6), 7.74 (td, *J* = 7.8, $^4J_{HH}$ = 1.7 Hz, 1H, CH^7), 7.41 (br. d, *J* = 9.4 Hz, 1H, CH^5), 7.14 (ddd, *J* = 7.95, 4.8, $^4J_{HH}$ = 1.0 Hz, 1H, CH^8), 7.02 (dd, *J* = 9.4, $^4J_{HH}$ = 2.0 Hz, 1H, CH^4), 6.43 (br. s, 1H, NH^{10}), 4.64 (s, 2H, CH_2^2), 3.69 (br. t, *J* = 4.4 Hz, 4H, CH_2^{14}), 3.15 (t, *J* = 5.9 Hz, 2H, CH_2^{11}), 2.57 (t, *J* = 5.9 Hz, 2H, CH_2^{12}), 2.45 (br. t, *J* = 4.4 Hz, 4H, CH_2^{13}), 2.45 (br. s, 1H, OH^3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.9 (C^{4a}), 148.5 (C^9H), 140.4 (C^{2a}), 136.7 (C^7H), 132.2 (C^{3a}), 130.0 (C^{1a}), 125.4 (C^8H), 123.9 (C^{5a}), 121.2 (C^4H), 120.3 (C^1H + C^6H), 117.6 (C^5H), 67.0 ($C^{14}H_2$), 62.7 (C^2H_2), 58.4 ($C^{12}H_2$), 53.6 ($C^{13}H_2$), 43.6 ($C^{11}H_2$).

LCMS (High pH, UV, ESI): R_t = 0.73 min, $[M+H]^+$ m/z 354.3.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{19}H_{24}N_5O_2$: 354.1930, found: 354.1941.

4-(6-Methoxy-3-(((trimethylsilyl)methyl)amino)imidazo[1,2-a]pyridin-2-yl)phenol 4h



4h

The reaction was performed according to **General Procedure C**, using 5-methoxy-2-aminopyridine **1d** (124 mg, 1.00 mmol), 4-hydroxybenzaldehyde **2g** (244 mg, 2.00 mmol) and (isocyanomethyl)trimethylsilane **3e** (282 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 92% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography using a 40 g Biotage RediSep silica cartridge, with an elution gradient of 10 % ethyl acetate in cyclohexane to 40 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford 4-(6-methoxy-3-(((trimethylsilyl)methyl)amino)imidazo[1,2-a]pyridin-2-yl)phenol **4h** (261 mg, 0.764 mmol, 76 % yield) as a red-orange powder.

mp: 196-197 °C (dec.)

IR ν_{max} (cm^{-1}): 1609, 1505, 1242, 837, 526.

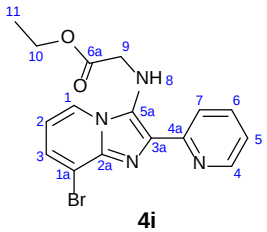
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 9.41 (br. s, 1H, OH^7), 7.93-7.88 (m, 2H, CH^5 + CH^9), 7.68 (d, *J* = 1.5 Hz, 1H, CH^1), 7.36 (dd, *J* = 9.4, $^5J_{HH}$ = 1.0 Hz, 1H, CH^4), 6.93 (dd, *J* = 9.4, $^4J_{HH}$ = 2.5 Hz, 1H, CH^3), 6.83-6.78 (d, *J* = 7.9 Hz, 2H, CH^6 + CH^8), 4.27 (t, *J* = 5.9, 1H, CH^{10}), 3.82 (s, 3H, $CH_3{}^2$), 2.44 (d, *J* = 5.9 Hz, 2H, $CH_3{}^{11}$), 0.08 (s, 9H, $CH_3{}^{12}$).

^{13}C NMR (101 MHz, DMSO-*d*$_6$): δ 156.3 (C^{5a}), 147.9 (C^{1a}), 137.1 (C^{2a}), 134.9 (C^{6a}), 128.6 (C^{3a}), 127.6 (C^5H + C^9H), 125.9 (C^{4a}), 117.7 (C^3H), 116.9 (C^4H), 115.0 (C^6H + C^8H), 104.4 (C^1H), 55.9 (C^2H_3), 37.3 ($C^{11}H_2$), -2.55 ($C^{12}H_3$).

LCMS (High pH, UV, ESI): R_t = 1.14 min, $[M+H]^+$ m/z 342.2.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{18}H_{24}N_3O_2Si$: 342.1638, found: 342.1638.

Ethyl 2-((8-bromo-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-yl)amino)acetate 4i



4i

The reaction was performed according to **General Procedure C**, using 3-bromo-2-aminopyridine **1e** (174 mg, 1.00 mmol), picolinaldehyde **2f** (190 µL, 2.00 mmol) and ethyl 2-isocyanoacetate **3h** (219 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 44% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography using a 40 g Biotage RediSep silica cartridge, with an elution gradient of cyclohexane to 40 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford ethyl 2-((8-bromo-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-yl)amino)acetate **4i** (159 mg, 0.424 mmol, 42 % yield) as an orange oil.

Analytically pure sample prepared *via* MDAP isolation (High pH), Method C, 20 min run. This afforded the desired product as a pale yellow solid.

mp: 90-91 °C

IR ν_{max} (cm^{-1}): 1609, 1505, 1242, 837, 526.

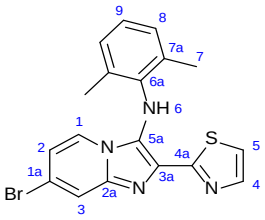
^{1}H NMR (400 MHz, CD_3Cl): δ 8.60-8.56 (m, 1H, CH^4), 8.30 (app. dt, *J* = 8.0, $^4J_{HH}$ = 1.2 Hz, 1H, CH^7), 8.09 (dd, *J* = 6.9, $^4J_{HH}$ = 1.0 Hz, 1H, CH^1), 7.76 (td, *J* = 7.4, $^4J_{HH}$ = 2.0 Hz, 1H, CH^6), 7.39 (dd, *J* = 6.9, $^4J_{HH}$ = 1.0 Hz, 1H, CH^3), 7.17 (ddd, *J* = 7.4, 4.9, $^4J_{HH}$ = 1.2 Hz, 1H, CH^5), 6.67 (t, *J* = 7.1 Hz, 1H, CH^2), 6.55 (br. s, 1H, NH^8), 4.16 (q, *J* = 7.4 Hz, 2H, $CH_2{}^{10}$), 3.88 (s, 2H, $CH_2{}^9$), 1.20 (t, *J* = 7.4 Hz, 3H, $CH_3{}^{11}$).

^{13}C NMR (101 MHz, CD_3Cl): δ 170.7 (C^{6a}), 154.2 (C^{4a}), 148.7 (C^4H), 138.5 (C^{2a}), 136.6 (C^6H), 131.8 (C^{5a}), 131.7 (C^{3a}), 126.0 (C^3H), 122.1 (C^1H), 121.7 (C^5H), 121.1 (C^7H), 112.2 (C^{1a}), 112.0 (C^2H), 61.2 ($C^{10}H_2$), 48.7 (C^9H_2), 14.1 ($C^{11}H_3$).

LCMS (High pH, UV, ESI): R_t = 1.10 min, [M] m/z 374.9.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{16}H_{16}{}^{79}BrN_4O_2$: 375.0457, found: 375.0449. m/z calculated for $[M+H]^+$ $C_{16}H_{16}{}^{81}BrN_4O_2$: 377.0436, found: 377.0427.

7-Bromo-*N*-(2,6-dimethylphenyl)-2-(thiazol-2-yl)imidazo[1,2-a]pyridin-3-amine 4j



4j

The reaction was performed according to **General Procedure C**, using 4-bromo-2-aminopyridine **1f** (173 mg, 1.00 mmol), thiazole-2-carbaldehyde **2e** (0.176 µL, 2.00 mmol) and 2,6-dimethylphenylisocyanide **3b** (262 mg, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 65% of the starting material had been consumed in the reaction. The reaction mixture was then passed through an Isolute® 5 g aminopropyl frit, washing with 20 mL methanol, and concentrated *in vacuo*. The crude product was then purified by flash column chromatography using a 40 g Biotage RediSep silica cartridge, with an elution gradient of cyclohexane to 40 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford 7-Bromo-*N*-(2,6-dimethylphenyl)-2-(thiazol-2-yl)imidazo[1,2-a] pyridin-3-amine **4j** (185 mg, 0.463 mmol, 46 % yield) as a beige powder.

mp: 208-209 °C (dec.)

IR ν_{max} (cm^{-1}): 3273, 2917, 1616, 1570, 1524, 1472.

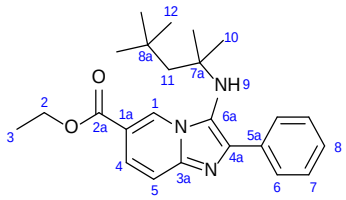
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (br. s, 1H, NH^6), 7.82 (d, *J* = 3.0 Hz, 1H, CH^4), 7.66 (br. d, *J* = 2.0 Hz, 1H, CH^3), 7.27 (d, *J* = 3.0 Hz, 1H, CH^5), 7.11 - 7.08 (m, 3H, CH^8, CH^9), 6.86 (dd, $^4J_{HH}$ = 7.6, $^5J_{HH}$ =1.0 Hz, 1H, CH^1), 6.50 (dd, *J* = 7.6, $^4J_{HH}$ = 2.0 Hz, 1H, CH^2), 2.14 (s, 6H, $CH_3{}^7$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.3 (C^{4a}), 143.0 (C^4H), 139.6 (C^{2a}), 136.7 (C^{5a}), 135.3 (C^{7a}), 129.6 (C^{3a}), 129.0 (C^8H), 126.3 (C^9H), 122.5 (C^1H + C^{6a}), 120.1 (C^3H), 116.9 (C^5H), 116.2 (C^{1a}), 116.0 (C^2H), 18.7 (C^7H_3).

LCMS (High pH, UV, ESI): R_t = 1.42 min, $[M+H]^+$ m/z 401.0.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{18}H_{16}{}^{79}BrN_4S$: 399.0279, found: 399.0262. m/z calculated for $[M+H]^+$ $C_{18}H_{16}{}^{81}BrN_4S$: 401.0259, found: 401.0341.

Ethyl 2-phenyl-3-((2,4,4-trimethylpentan-2-yl)amino)imidazo[1,2-a]pyridine-6-carboxylate 4k



4k

The reaction was performed according to **General Procedure C**, using ethyl-6-aminonicotinate **1g** (166 mg, 1.00 mmol), benzaldehyde **2a** (203 µL, 2.00 mmol) and 1,1,3,3-tetramethylbutylisocyanide **3d** (351 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 67% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography using a 40 g Biotage RediSep silica cartridge, with an elution gradient of 5 % ethyl acetate in cyclohexane to 30 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford ethyl 2-phenyl-3-((2,4,4-trimethylpentan-2-yl)amino)imidazo[1,2-a] pyridine-6-carboxylate **4k** (247 mg, 0.628 mmol, 63 % yield) as a yellow flaky solid.

mp: 118-119 °C (dec.)

IR ν_{max} (cm^{-1}): 3327, 2958, 1715, 1291, 1102, 695.

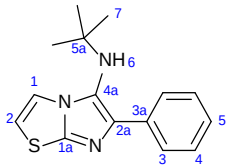
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05-9.03 (m, 1H, CH^1), 7.87-7.83 (m, 2H, CH^6), 7.69 (dd, J = 9.3, $^4J_{HH}$ = 1.5 Hz, 1H, CH^4), 7.52 (d, J = 9.3 Hz, 1H, CH^5), 7.45 (t, J = 7.5, 2H, CH^7), 7.35 (br. t, J = 7.5, 1H, CH^8), 4.43 (q, J = 7.2, 2H, CH_2^2), 3.28 (br. s, 1H, NH^9), 1.60 (s, 2H, CH_2^{11}), 1.43 (t, J = 7.2 Hz, 3H, CH_3^3), 1.06 (s, 9H, CH_3^{12}), 0.96 (s, 6H, CH_3^{10}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3 (C^{2a}), 142.5 (C^{3a}), 141.5 (C^{6a}), 134.9 (C^{5a}), 128.4 (C^6H, C^7H, C^9H + $C^{10}H$), 128.0 (C^8H), 127.8 (C^1H), 124.4 (C^{4a}), 123.6 (C^5H), 116.6 (C^4H), 115.7 (C^{1a}), 61.3 (C^{7a}), 60.8 (C^2H_2), 57.0 ($C^{14}H_2$), 31.9 ($C^{15}H_3$, $C^{16}H_3$ + $C^{17}H_3$), 31.8 (C^{8a}), 29.1 ($C^{12}H_3$ + $C^{13}H_3$), 14.4 (C^3H_3).

LCMS (High pH, UV, ESI): R_t = 1.53 min, $[M+H]^+$ m/z 394.4.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{24}H_{32}N_3O_2$: 394.2495, found: 394.2492.

***N*-(*tert*-Butyl)-6-phenylimidazo[2,1-b]thiazol-5-amine 4l**



4l

The reaction was performed according to **General Procedure C**, using 2-aminothiazole **1h** (100 mg, 1.00 mmol), benzaldehyde **2a** (203 µL, 2.00 mmol) and *N*-*tert*-butylisocyanide **3a** (226 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 51% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography using an 80 g Biotage RediSep silica cartridge, with an elution gradient of cyclohexane to 10 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford *N*-(*tert*-butyl)-6-phenylimidazo[2,1-b]thiazol-5-amine **4l** (122 mg, 0.450 mmol, 45 % yield) as a white powder.

mp: 159-160 °C.

IR ν_{max} (cm^{-1}): 3329, 2963, 1441, 1359, 1179, 645.

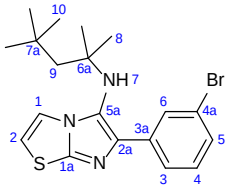
^{1}H NMR (400 MHz, CD_3Cl): δ 7.90-7.86 (m, 2H, CH^3), 7.41-7.37 (m, 2H, CH^4), 7.37-7.35 (m, 1H, CH^1), 7.25 (tt, J = 7.4, $^4J_{HH}$ = 1.3 Hz, 1H, CH^5), 6.72 (d, J = 4.4 Hz, 1H, CH^2), 3.05 (br. s, 1H, NH^6), 1.07 (s, 9H, CH_3^7).

^{13}C NMR (101 MHz, CD_3Cl): δ 145.5 (C^{1a}), 140.2 (C^{4a}), 135.3 (C^{3a}), 128.2 (C^3H), 127.2 (C^4H), 126.7 (C^5H), 125.5 (C^{2a}), 117.8 (C^1H), 111.4 (C^2H), 55.8 (C^{5a}), 30.2 (C^7H_3).

LCMS (High pH, UV, ESI): R_t = 1.16 min, $[M+H]^+$ m/z 272.1.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{15}H_{18}N_3S$: 272.1221, found: 272.1221.

6-(3-Bromophenyl)-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[2,1-b]thiazol-5-amine 4m



4m

The reaction was performed according to **General Procedure C**, using 2-aminothiazole **1h** (100 mg, 1.00 mmol), 3-bromobenzaldehyde **2c** (233 µL, 2.00 mmol) and 1,1,3,3-tetramethylbutylisocyanide **3d** (351 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 87% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography using an 80 g Biotage RediSep silica cartridge, with an elution gradient of cyclohexane to 20 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford 6-(3-bromophenyl)-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[2,1-b]thiazol-5-amine **4m** (279 mg, 0.687 mmol, 69 % yield) as a colourless oil.

IR ν_{max} (cm^{-1}): 3273, 2951, 1595, 1476, 1365, 693.

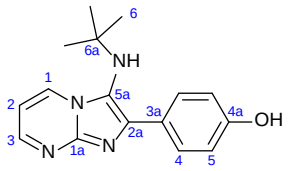
^{1}H NMR (400 MHz, CD_3Cl): δ 8.12 (t, *J* = 2.0 Hz, 1H, CH^{3}), 7.82 (dt, *J* = 7.9, $^{4}J_{HH}$ = 1.5 Hz, 1H, $C^{5}H$), 7.39-7.36 (m, 2H, $C^{1}H$ + $C^{6}H$), 7.24 (t, *J* = 7.9 Hz, 1H, $C^{4}H$), 6.75 (d, *J* = 4.4 Hz, 1H, $C^{2}H$), 3.03 (br. s, 1H, NH^{7}), 1.57 (s, 2H, $C^{9}H_2$), 1.05 (s, 9H, $C^{10}H_3$), 1.04 (s, 6H, $C^{8}H_3$).

^{13}C NMR (101 MHz, CD_3Cl): δ 145.8 (C^{1a}), 139.0 (C^{5a}), 137.5 (C^{3a}), 130.3 ($C^{3}H$), 129.7 ($C^{4}H$), 129.6 ($C^{6}H$), 125.8 ($C^{5}H$), 125.6 (C^{2a}), 122.3 (C^{4a}), 117.8 ($C^{1}H$), 111.8 ($C^{2}H$), 60.1 ($C^{9}H_2$), 57.0 (C^{6a}), 31.9 ($C^{8}H_3$), 31.8 (C^{7a}), 29.2 ($C^{10}H_3$).

LCMS (High pH, UV, ESI): R_t = 1.55 min, $[M+H]^+$ m/z 406.2.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{19}H_{25}{}^{79}BrN_3S$: 406.0953, found: 406.0947. m/z calculated for $[M+H]^+$ $C_{19}H_{25}{}^{81}BrN_3S$: 408.0932, found: 408.0930.

4-(3-(*tert*-Butylamino)imidazo[1,2-a]pyrimidin-2-yl)phenol 4n



4n

The reaction was performed according to **General Procedure C**, using 2-aminopyrimidine **1i** (95 mg, 1.00 mmol), 4-hydroxybenzaldehyde **2g** (244 mg, 2.00 mmol) and *N-tert*-butylisocyanide **3a** (226 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 32% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography using a 55 g aminopropyl RediSep silica cartridge, with an elution gradient of cyclohexane to neat ethyl acetate. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford 4-(3-(*tert*-butylamino)imidazo[1,2-a]pyrimidin-2-yl)phenol **4n** (93 mg, 0.329 mmol, 33 % yield) as a yellow-orange powder.

The product was formed as a mixture of 2 regioisomers: approximately 92% of **4n** along with ca. 8 % **4n'** by ^{1}H and ^{1}D NOESY NMR spectroscopic analysis (see below).

Product 4n:

mp: 185-186 °C (dec.)

IR ν_{max} (cm^{-1}): 3116, 2966, 1611, 1506, 1365, 848, 759.

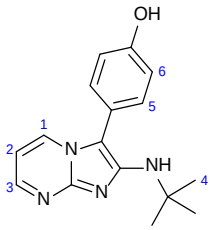
^{1}H NMR (400 MHz, CD_3OD): δ 8.76 (dd, *J* = 6.8, $^{4}J_{HH}$ = 2.0 Hz, 1H, CH^{1}), 8.45 (dd, *J* = 4.3, $^{4}J_{HH}$ = 2.0 Hz, 1H, CH^{3}), 7.88-7.83 (m, 2H, CH^{4}), 7.00 (dd, *J* = 6.8, 4.0 Hz, 1H, CH^{2}), 6.89-6.85 (m, 2H, CH^{5}), 1.03 (s, 9H, $CH_3{}^{6}$).

^{13}C NMR (101 MHz, CD_3OD): δ 158.7 (C^{4a}), 150.8 ($C^{3}H$), 146.1 (C^{1a}), 142.0 (C^{5a}), 133.3 ($C^{1}H$), 131.1 ($C^{4}H$), 126.8 (C^{2a}), 123.4 (C^{3a}), 116.1 ($C^{5}H$), 109.4 ($C^{2}H$), 57.0 (C^{6a}), 30.6 ($C^{6}H_3$).

LCMS (High pH, UV, ESI): R_t = 0.83 min, $[M+H]^+$ m/z 283.2.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{16}H_{19}N_4O$: 283.1545, found: 283.1555.

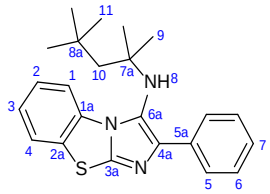
Regioisomer 4n'



4n'

^{1}H NMR (400 MHz, CD_3OD): δ 8.39 (dd, *J* = 6.6, $^{4}J_{HH}$ = 2.0 Hz, 1H, CH^{3}), 8.20 (dd, *J* = 4.5, $^{4}J_{HH}$ = 2.0 Hz, 1H, CH^{1}), 7.34-7.29 (m, 2H, CH^{5}), 6.99-6.97 (m, 2H, CH^{6}), 6.82-6.79 (m, 1H, CH^{2}), 1.42 (s, 9H, $CH_3{}^{4}$).

2-Phenyl-*N*-(2,4,4-trimethylpentan-2-yl)benzo[d]imidazo[2,1-b]thiazol-3-amine 4o



4o

The reaction was performed according to **General Procedure C**, using 2-aminobenzothiazole **1j** (150 mg, 1.00 mmol), benzaldehyde **2a** (203 µL, 2.00 mmol) and 1,1,3,3-tetramethylbutylisocyanide **3d** (351 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 39% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography using an 80 g RediSep silica cartridge, with an elution gradient of 10 % ethyl acetate in cyclohexane to 25% ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford 2-phenyl-*N*-(2,4,4-trimethylpentan-2-yl)benzo[d]imidazo[2,1-b]thiazol-3-amine **4o** (149 mg, 0.395 mmol, 40 % yield) as a white crystalline solid.

mp: 132-133 °C.

IR ν_{max} (cm^{-1}): 3272, 2950, 1487, 1191, 753, 697.

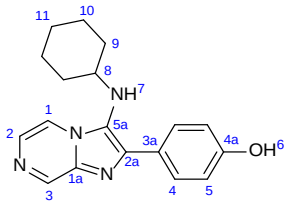
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (br. dd, J = 8.0, $^4J_{HH}$ = 0.8 Hz, 1H, CH^4), 7.97 (dd, J = 8.0, $^4J_{HH}$ = 1.0 Hz, 1H, CH^1), 7.95-7.92 (m, 2H, CH^5), 7.54 (ddd, J = 8.3, 7.3, $^4J_{HH}$ = 1.3 Hz, 1H, CH^3), 7.41-7.36 (m, 3H, CH^2, CH^6), 7.26 (tt, J = 7.3, $^4J_{HH}$ = 1.8 Hz, 1H, CH^7), 4.60 (s, 1H, NH^8), 1.57 (s, 2H, CH_2^{10}), 0.95 (s, 6H, CH_3^9), 0.89 (s, 9H, CH_3^{11}).

^{13}C NMR (101 MHz, DMSO-d_6): δ 142.6 (C^{3a}), 140.6 (C^{6a}), 135.3 (C^{1a}), 133.1 (C^{5a}), 129.1 (C^{2a}), 128.2 (C^{4a}), 127.8 (C^6H), 127.7 (C^5H), 126.6 (C^7H), 125.7 (C^3H), 124.6 (C^1H), 124.4 (C^2H), 114.5 (C^4H), 59.8 (C^{7a}), 56.0 ($C^{10}H_2$), 31.5 ($C^{11}H_3$), 30.9 (C^{8a}), 28.0 (C^9H_3).

LCMS (High pH, UV, ESI): R_t = 1.61 min, $[M+H]^+$ m/z 378.3.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{23}H_{28}N_3S$: 378.2004, found: 378.2003.

4-(3-(Cyclohexylamino)imidazo[1,2-a]pyrazin-2-yl)phenol 4p



4p

The reaction was performed according to **General Procedure C**, using aminopyrazine **1k** (95 mg, 1.00 mmol), 4-hydroxybenzaldehyde **2g** (244 mg, 2.00 mmol) and cyclohexylisocyanide **3i** (249 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 60% of the starting material had been consumed in the reaction. The reaction mixture was passed through a 5 g aminopropyl frit, washing with 20 mL methanol, and dried *in vacuo*. The crude product was then purified by flash column chromatography using a 40 g RediSep silica cartridge, with an elution gradient of 20 % ethyl acetate in cyclohexane to 90 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford 4-(3-(cyclohexylamino)imidazo[1,2-a]pyrazin-2-yl)phenol **4p** (166 mg, 0.539 mmol, 54 % yield) as a pale yellow powder.

mp: 284-285 °C (dec.)

IR ν_{max} (cm^{-1}): 3298, 2921, 1611, 1495, 1283, 832, 796.

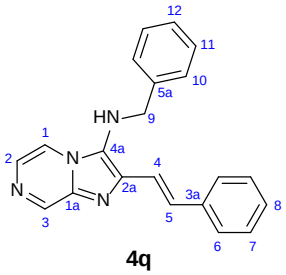
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.59 (br. s, 1H, OH^6), 8.84 (d, *J* = 1.5 Hz, 1H, CH^3), 8.31 (dd, *J* = 4.9, $^4J_{HH}$ = 1.5 Hz, 1H, CH^2), 8.06-8.02 (m, 2H, CH^4), 7.81 (d, *J* = 4.4 Hz, 1H, CH^1), 6.87-6.82 (m, 2H, CH^5), 4.89 (d, *J* = 6.4 Hz, 1H, NH^9), 2.91-2.80 (m, 1H, CH^8), 1.73-1.60 (m, 4H, $CH_2{}^9{}_{ax}$, $CH_2{}^{10}{}_{ax}$), 1.53-1.47 (m, 1H, $CH_2{}^{11}$), 1.33-1.21 (m, 2H, $CH_2{}^9{}_{eq}$), 1.16-1.02 (m, 3H, $CH_2{}^{10}{}_{eq}$, $CH_2{}^{11}$).

^{13}C NMR (101 MHz, DMSO-d_6): δ 157.2 (C^{4a}), 141.8 (C^3H), 137.3 (C^{1a}), 135.7 (C^{5a}), 128.3 (C^1H), 128.1 (C^4H), 126.1 (C^{2a}), 124.7 (C^{3a}), 116.1 (C^2H), 115.2 (C^5H), 56.2 (C^8H), 33.6 (C^9), 25.3 ($C^{11}H_2$), 24.5 (C^{10}).

LCMS (High pH, UV, ESI): R_t = 0.96 min, $[M+H]^+$ m/z 309.3.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{18}H_{21}N_4O$: 309.1710, found: 309.1697.

(*E*)-*N*-Benzyl-2-styrylimidazo[1,2-a]pyrazin-3-amine 4q



4q

The reaction was performed according to **General Procedure C**, using aminopyrazine **1k** (95 mg, 1.00 mmol), cinnamaldehyde **2g** (252 µL, 2.00 mmol) and *N*-benzylisocyanide **3j** (244 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 56% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography using an 80 g RediSep silica cartridge, with an elution gradient of 20 % ethyl acetate in cyclohexane to 80 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford (*E*)-*N*-benzyl-2-styrylimidazo[1,2-a]pyrazin-3-amine **4q** (149 mg, 0.457 mmol, 46 % yield) as a yellow powder.

An analytically pure sample was prepared *via* MDAP isolation (High pH), Method B, 20 min run.

mp: 148-149 °C.

IR ν_{max} (cm^{-1}): 3312, 1526, 1350, 966, 784, 748, 685.

^{1}H NMR (400 MHz, CD_3Cl): δ 8.94 (d, *J* = 1.5 Hz, 1H, CH^3), 7.79 (dd, *J* = 4.4, $^4J_{HH}$ = 1.5 Hz, 1H, CH^2), 7.76 (d, *J* = 4.9, 1H, CH^1), 7.59 (d, *J* = 16.2 Hz, 1H, CH^4), 7.49-7.45 (m, 2H, CH^6), 7.38-7.33 (m, 4H, CH^7, CH^{11}), 7.32-7.27 (m, 4H, CH^8, CH^{10}, CH^{12}), 6.92 (d, *J* = 16.2 Hz, 1H, CH^5), 4.26 (s, 2H, $CH_2{}^9$).

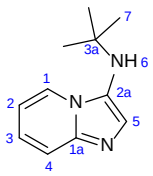
^{13}C NMR (101 MHz, CD_3Cl): δ 143.1 (C^3H), 138.9 (C^{4a}), 138.2 (C^{1a}), 137.4 (C^{5a}), 137.1 (C^{3a}), 132.0 (C^5H), 129.1 (C^7H), 129.0 (C^2H), 128.8 (C^6H), 128.4 (C^{11}), 128.2 (C^8H, $C^{12}H$), 128.0 (C^4H), 126.9 ($C^{10}H$), 117.3 (C^1H), 115.2 (C^{2a}), 53.3 (C^9H_2).

LCMS (High pH, UV, ESI): R_t = 1.13 min, $[M+H]^+$ m/z 327.1.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{21}H_{19}N_4$: 327.1604, found: 327.1588.

The spectroscopic data is in accordance with that reported in the literature.[3]

***N*-(*tert*-Butyl)imidazo[1,2-a]pyridin-3-amine 4r**



4r

The reaction was performed according to **General Procedure D**, using 2-aminopyridine **1a** (94 mg, 1.00 mmol), formaldehyde **2h** (37 % wt. solution in H_2O, 83 µL, 1.12 mmol) and *N*-*tert*-butylisocyanide **3a** (226 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 94% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography using a 40 g RediSep silica cartridge, with an elution gradient of ethyl acetate to 20 % ethanol in ethyl acetate. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford *N*-(*tert*-butyl)imidazo[1,2-a]pyridin-3-amine **4r** (155 mg, 0.819 mmol, 82 % yield) as an off-white powder.

mp: 119-120 °C (lit.[4] 118-120 °C)

IR ν_{max} (cm^{-1}): 3230, 2969, 1630, 1548, 1503, 1336, 1229, 758.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (br. d, *J* = 6.9 Hz, 1H, CH^1), 7.52 (br. dd, *J* = 7.5, $^4J_{HH}$ = 1.0 Hz, 1H, CH^4), 7.32 (s, 1H, CH^5), 7.14-7.09 (m, 1H, CH^3), 6.77 (t, *J* = 6.6 Hz, 1H, CH^2), 2.59 (br. s, 1H, NH^6), 1.20 (s, 9H, $CH_3{}^7$).

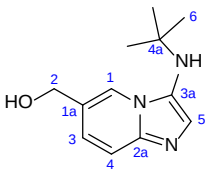
^{13}C NMR (101 MHz, $CDCl_3$): δ 142.7 (C^{1a}), 128.7 (C^3H), 127.1 (C^{2a}), 123.6 (C^1H), 123.0 (C^5H), 117.5 (C^4H), 111.4 (C^2H), 53.9 (C^{3a}), 29.7 (C^7H_3).

LCMS (High pH, UV, ESI): R_t = 0.87 min, $[M+H]^+$ m/z 190.1.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{11}H_{16}N_3$: 190.1344, found: 190.1347.

The spectroscopic data is in accordance with that reported in the literature.

(3-(*tert*-Butylamino)imidazo[1,2-a]pyridin-6-yl)methanol 4s



4s

The reaction was performed according to **General Procedure D**, using (6-aminopyridin-3-yl)methanol **1c** (124 mg, 1.00 mmol), formaldehyde **2h** (37 % wt. solution in H_2O, 83 µL, 1.12 mmol) and *N-tert*-butylisocyanide **3a** (226 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 94% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography using a 40 g RediSep silica cartridge, with an elution gradient of ethyl acetate to 10 % ethanol in ethyl acetate. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford (3-(*tert*-butylamino)imidazo[1,2-a]pyridin-6-yl)methanol **4s** (192 mg, 0.876 mmol, 88 % yield) as a white crystalline solid.

mp: 111-112 °C.

IR ν_{max} (cm^{-1}): 3314, 3149, 2968, 2844, 1213, 1049, 822.

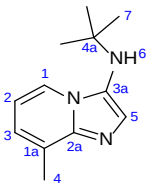
^{1}H NMR (400 MHz, CD_3OD): δ 8.34-8.31 (m, 1H, CH^1), 7.41 (dd, J = 9.1, $^5J_{HH}$ = 1.0 Hz, 1H, CH^4), 7.23 (dd, J = 9.1, $^4J_{HH}$ = 2.0 Hz, 1H, CH^3), 7.20 (s, 1H, CH^5), 4.64 (d, J = 1.0 Hz, 2H, $CH_2{}^2$), 1.20 (s, 9H, $CH_3{}^6$).

^{13}C NMR (101 MHz, CD_3OD): δ 143.1 (C^{2a}), 129.9 (C^{3a}), 127.7 (C^5H), 127.3 (C^{1a}), 126.1 (C^3H), 122.1 (C^1H), 117.1 (C^4H), 62.7 (C^2H_2), 54.4 (C^{4a}), 29.8 (C^6H_3).

LCMS (High pH, UV, ESI): R_t = 0.68 min, $[M+H]^+$ 220.2 m/z.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{12}H_{18}N_3O$: 220.1450, found: 220.1454.

***N*-(*tert*-Butyl)-8-methylimidazo[1,2-a]pyridin-3-amine 4t**



4t

The reaction was performed according to **General Procedure D**, using 3-methyl-2-aminopyridine **1b** (108 mg, 1.00 mmol), formaldehyde **2h** (37 % wt. solution in H_2O, 83 µL, 1.12 mmol) and *N*-*tert*-butylisocyanide **3a** (226 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 94% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the desired product was purified by flash column chromatography using a 40 g RediSep silica cartridge, with an elution gradient of 50 % ethyl acetate in cyclohexane to neat ethyl acetate. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford *N*-(*tert*-butyl)-8-methylimidazo[1,2-a]pyridin-3-amine **4t** (177 mg, 0.871 mmol, 87 % yield) as a white crystalline solid.

An analytically pure sample was prepared *via* MDAP isolation (High pH), Method B, 30 min run.

mp: 90-91 °C.

IR ν_{max} (cm^{-1}): 3217, 2972, 1542, 1354, 750.

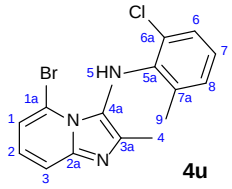
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (br. d, *J* = 6.8 Hz, 1H, CH^1), 7.31 (s, 1H, CH^5), 6.94-6.91 (m, 1H, CH^3), 6.70 (t, *J* = 6.8 Hz, 1H, CH^2), 2.77 (br. s, 1H, NH^6), 2.59 (s, 3H, $CH_3{}^4$), 1.19 (s, 9H, $CH_3{}^7$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.9 (C^{2a}), 127.9 (C^3H), 127.5 (C^{3a}), 127.0 (C^{1a}), 122.6 (C^1H), 121.0 (C^5H), 111.6 (C^2H), 53.8 (C^{4a}), 29.7 (C^7H_3), 16.5 (C^4H_3).

LCMS (High pH, UV, ESI): R_t = 0.93 min, $[M+H]^+$ 204.2 m/z.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{12}H_{18}N_3$: 204.1501, found: 204.1501.

5-Bromo-*N*-(2-chloro-6-methylphenyl)-2-methylimidazo[1,2-a]pyridin-3-amine 4u



4u

A stock solution of 6-bromo-2-aminopyridine **1l** (346 mg, 2.00 mmol), and acetaldehyde **2i** (336 µL, 6.00 mmol) was prepared in ethanol (10 mL total solution volume). Then, a solution of 2-chloro-6-methylphenylisocyanide **3c** (606 mg, 4 mmol) and HCl (160 µL, 1.25 M solution in ethanol, 0.200 mmol) was prepared in ethanol (10 mL total solution volume). The flow reactor was heated to 130 °C whilst pumping clean ethanol through the system at a flow rate of 0.100 mL/min/line. Once at temperature, each of the two input lines was placed into one of the two stock solutions, and the reagents were pumped at 0.100 mL/min/line for 50 min (5 mL removed from each solution). The input lines were changed back to the solvent reservoir and pumped to waste for 25 min to account for the dead volume in the reactor. The desired product solution was then collected for 61.75 min (12.4 mL collected), after which time the flow reactor was cooled and turned off. Following the reaction, a 10 µL aliquot of the crude product solution was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 96% of the starting material had been consumed in the reaction. The crude reaction solution was concentrated *in vacuo*, and the desired product was purified by flash column chromatography using an 80 g RediSep silica cartridge, with an elution gradient of 15 % ethyl acetate in cyclohexane to 30 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford 5-bromo-*N*-(2-chloro-6-methyl phenyl)-2-methylimidazo[1,2-a]pyridin-3-amine **4u** (227 mg, 0.647 mmol, 65 % yield) as a brown powder.

mp: 158-159 °C.

IR ν_{max} (cm^{-1}): 3359, 3239, 1591, 1466, 1305, 1119, 756.

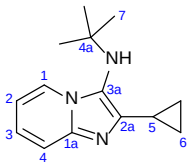
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 7.8, $^4J_{HH}$ = 2.5 Hz, 1H, CH^3), 7.24 (dd, *J* = 7.8, 1.0 Hz, 1H, CH^2), 7.03-6.97 (m, 2H, CH^1 + CH^6), 6.94 (br. d, *J* = 7.8 Hz, 1H, CH^8), 6.76 (t, *J* = 7.8 Hz, 1H, CH^7), 5.88 (br. s, 1H, NH^5), 2.10 (d, *J* = 1.0 Hz, 3H, $CH_3{}^9$), 1.66 (s, 3H, $CH_3{}^4$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.7 (C^{2a}), 140.3 (C^{5a}), 139.8 (C^{1a}), 131.0 (C^2H), 127.6 (C^8H), 126.8 (C^{4a}), 124.4 (C^1H), 122.6 (C^{3a}), 122.5 (C^{7a}), 120.8 (C^6H), 118.6 (C^3H), 116.4 (C^7H), 112.2 (C^{6a}), 18.7 (C^9H_3), 12.8 (C^4H_3).

LCMS (High pH, UV, ESI): R_t = 1.23 min, $[M+H]^+$ 350.1 m/z.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{15}H_{14}{}^{79}Br^{35}ClN_3$: 350.0060, found: 350.0061. m/z calculated for $[M+H]^+$ $C_{15}H_{14}{}^{79}Br^{37}ClN_3$: 352.0030; m/z calculated for $C_{15}H_{14}{}^{81}Br^{35}ClN_3$: 352.0039; found: 352.0041. m/z calculated for $[M+H]^+$ $C_{15}H_{14}{}^{81}Br^{37}ClN_3$: 354.0010, found: 354.0014.

_N_-(_tert_-Butyl)-2-cyclopropylimidazo[1,2-a]pyridin-3-amine 4v



4v

The reaction was performed according to **General Procedure D**, using 2-aminopyridine **1a** (124 mg, 1.00 mmol), cyclopropanecarbaldehyde **2j** (149 µL, 2.00 mmol) and *N*-*tert*-butylisocyanide **3a** (226 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that >99% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo* to afford *N*-(*tert*-butyl)-2-cyclopropylimidazo[1,2-a]pyridin-3-amine **4v** (206 mg, 0.898 mmol, 90 % yield) as a white crystalline solid.

mp: 56-57 °C.

IR ν_{max} (cm^{-1}): 3253, 2966, 1329, 1205, 754.

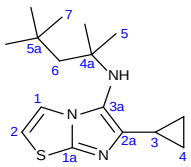
^{1}H NMR (400 MHz, CD_3OD): δ 8.32-8.28 (m, 1H, CH^1), 7.34-7.29 (m, 1H, CH^4), 7.19 (ddd, J = 9.1, 6.6, $^4J_{HH}$ = 1.0 Hz, 1H, CH^3), 6.85 (td, J = 6.6, $^4J_{HH}$ = 1.5 Hz, 1H, CH^2), 2.20-2.12 (m, 1H, CH^5), 1.22 (s, 9H, $CH_3{}^7$), 1.00-0.94 (m, 4H, $CH_2{}^6$).

^{13}C NMR (101 MHz, CD_3OD): δ 142.6 (C^{1a}), 142.2 (C^{3a}), 125.8 (C^3H), 124.6 (C^1H), 120.8 (C^{2a}), 116.0 (C^4H), 112.6 (C^2H), 56.5 (C^{4a}), 30.6 (C^7H_3), 9.63 (C^5H), 8.73 (C^6H_2).

LCMS (High pH, UV, ESI): R_t = 1.04 min, $[M+H]^+$ 230.2 m/z.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{14}H_{20}N_3$: 230.1657, found: 230.1662.

6-Cyclopropyl-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[2,1-b]thiazol-5-amine 4w



4w

The reaction was performed according to **General Procedure D**, using 2-aminothiazole **1h** (100 mg, 1.00 mmol), cyclopropanecarbaldehyde **2j** (149 µL, 2.00 mmol) and 1,1,3,3-tetramethylbutylisocyanide **3d** (351 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see

Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that >99% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, before the desired product was purified by flash column chromatography using a 40 g RediSep silica cartridge, with an elution gradient of 10 % ethyl acetate in cyclohexane to 30 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford 6-cyclopropyl-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[2,1-b]thiazol-5-amine **4w** (246 mg, 0.844 mmol, 84 % yield) as a clear, brown oil.

IR ν_{max} (cm^{-1}): 2951, 1683, 1464, 1365, 653.

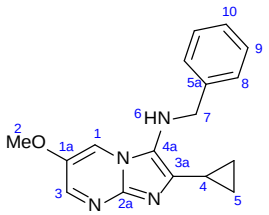
^{1}H NMR (400 MHz, CD_3OD): δ 7.52 (br. d, *J* = 4.5 Hz, 1H, CH^1), 6.94 (br. d, *J* = 4.5 Hz, 1H, CH^2), 2.02-1.90 (m, 1H, CH^3), 1.67 (s, 2H, CH_2^6), 1.21 (s, 6H, CH_3^5), 1.08 (s, 9H, CH_3^7), 0.88 - 0.78 (m, 4H, CH_2^4).

^{13}C NMR (101 MHz, CD_3OD): δ 146.0 (C^{1a}), 143.2 (C^{3a}), 127.3 (C^{2a}), 119.7 (C^1H), 112.0 (C^2H), 60.1 (C^{4a}), 57.2 (C^6H_2), 32.5 (C^{5a}), 32.4 (C^7H_3), 29.6 (C^5H_3), 9.91 (C^3H), 7.93 (C^4H_2).

LCMS (High pH, UV, ESI): R_t = 1.35 min, $[M+H]^+$ 292.3 m/z.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{16}H_{26}N_3S$: 292.1847, found: 292.1846.

***N*-Benzyl-2-cyclopropyl-6-methoxyimidazo[1,2-a]pyrimidin-3-amine 4x**



4x

The reaction was performed according to **General Procedure D**, using 5-methoxy-2-aminopyrimidine **1m** (125 mg, 1.00 mmol), cyclopropanecarbaldehyde **2j** (149 µL, 2.00 mmol) and *N*-benzylisocyanide **3j** (244 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 75% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography using an 80 g RediSep silica cartridge, with an elution gradient of 30 % ethyl acetate in cyclohexane to 60 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford *N*-benzyl-2-cyclopropyl-6-methoxyimidazo[1,2-a]pyrimidin-3-amine **4x** (176 mg, 0.598 mmol, 60 % yield) as a yellow-orange powder.

mp: 136-137 °C.

IR ν_{max} (cm^{-1}): 3268, 3004, 2922, 1569, 1466, 1209, 698.

^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 8.11 (d, *J* = 2.9 Hz, 1H, CH^{3}), 7.88 (d, *J* = 2.9 Hz, 1H, CH^{1}), 7.30 (br. d, *J* = 7.3 Hz, 2H, CH^{8}), 7.27 (br. t, *J* = 7.7 Hz, 2H, CH^{9}), 7.22 (br. t, *J* = 7.3 Hz, 1H, CH^{10}), 5.26 (t, *J* = 5.9 Hz, 1H, NH^{6}), 4.16 (d, *J* = 5.9 Hz, 2H, $C^{7}H_2$), 3.74 (s, 3H, $C^{2}H_3$), 2.03-1.98 (m, 1H, $C^{4}H$), 0.84-0.80 (m, 4H, $C^{5}H_2$).

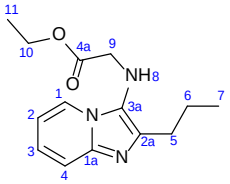
^{13}C NMR: (151 MHz, DMSO-*d*$_6$): δ 144.3 (C^{1a}), 140.6 ($C^{3}H$), 140.5 (C^{4a}), 140.4 (C^{2a}), 140.3 (C^{5a}), 128.3 ($C^{8}H$), 128.1 ($C^{9}H$), 126.9 ($C^{10}H$), 125.5 (C^{3a}), 111.2 ($C^{1}H$), 56.3 ($C^{2}H_3$), 51.9 ($C^{7}H_2$), 8.00 ($C^{5}H_2$), 7.91 ($C^{4}H$).

LCMS (High pH, UV, ESI): R_t = 0.95 min, $[M+H]^+$ 295.2 m/z.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{17}H_{19}N_4O$: 295.1559, found: 295.1559.

A single regioisomer was observed by ^{15}N HMBC spectroscopy.

Ethyl 2-((2-propylimidazo[1,2-a]pyridin-3-yl)amino)acetate 4y



4y

V

Preparation under flow conditions

The reaction was performed according to **General Procedure D**, using 2-aminopyridine **1a** (94 mg, 1.00 mmol), butyraldehyde **2k** (180 µL, 2.00 mmol) and ethyl 2-isocyanoacetate **3h** (219 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 93% of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, before the desired product was purified by flash column chromatography using an 80 g RediSep silica cartridge, with an elution gradient of 20 % ethyl acetate in cyclohexane to 70 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford ethyl 2-((2-propylimidazo[1,2-a]pyridin-3-yl)amino)acetate **4y** (215 mg, 0.823 mmol, 82 % yield) as a yellow oil.

IR ν_{max} (cm^{-1}): 3217, 2959, 2929, 1738, 1181, 753, 737.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (app. dt, *J* = 6.8, $^{4}J_{HH}$ = 1.5 Hz, 1H, CH^{1}), 7.45 (app. dt, *J* = 8.8, $^{4}J_{HH}$ = 1.0 Hz, 1H, CH^{4}), 7.08 (ddd, *J* = 8.8, 6.9, $^{4}J_{HH}$ = 1.5 Hz, 1H, CH^{3}), 6.75 (td, *J* = 6.9, $^{4}J_{HH}$ = 1.0 Hz, 1H, CH^{2}), 4.23 (q, *J* = 7.2 Hz, 2H, $CH_2{}^{10}$), 3.76 (d, *J* = 5.9 Hz, 2H, $CH_2{}^{9}$), 3.49 (br. t, *J* = 5.9 Hz, 1H, NH^{8}), 2.74 (dd, *J* = 7.3, 7.3 Hz, 2H, $CH_2{}^{5}$), 1.82-1.74 (m, 2H, $CH_2{}^{6}$), 1.28 (t, *J* = 7.2 Hz, 3H, $CH_3{}^{11}$), 0.99 (t, *J* = 7.3 Hz, 3H, $CH_3{}^{7}$).

^{13}C NMR: (101 MHz, $CDCl_3$): δ 171.9 (C^{4a}), 141.5 (C^{1a}), 139.4 (C^{3a}), 124.9 (C^{2a}), 123.2 ($C^{1}H$), 122.4 ($C^{3}H$), 117.0 ($C^{4}H$), 111.3 ($C^{2}H$), 61.3 ($C^{10}H_2$), 50.3 ($C^{9}H_2$), 29.2 ($C^{5}H_2$), 22.9 ($C^{6}H_2$), 14.2 ($C^{7}H_3$ + $C^{11}H_3$).

LCMS (High pH, UV, ESI): R_t = 0.90 min, $[M+H]^+$ 262.3 m/z.

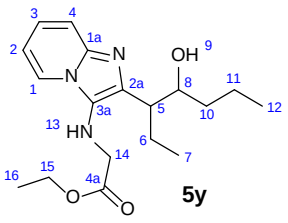
HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{14}H_{20}N_3O_2$: 262.1556, found: 262.1555.

Preparation under batch conditions:

The reaction was performed in batch mode using conditions reported in the patent literature.[5] To a 5 mL microwave vial was added a solution of 2-aminopyridine **1a** (94 mg, 1.00 mmol), butyraldehyde **2k** (99 µL, 1.10 mmol), ethyl 2-isocyanoacetate **3h** (131 µL, 1.20 mmol) and scandium (III) trifluoromethanesulfonate (25 mg, 0.050 mmol) in a mixture of methanol (1 mL) and dichloromethane (2 mL). The reaction mixture was stirred under ambient conditions for 144 h. During the course of the reaction, 10 µL aliquots were removed from the reaction mixture at 50 min, 24 h and 144 h time points, and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 28% of the starting material had been consumed in the reaction after 50 min, 38 % consumption was observed after 24 h, and 68 % was observed after 144 h. The reaction mixture was dried *in vacuo*, and purified by MDAP (High pH, Method B, 20 min run). The product-containing fractions were combined, and the solvent was removed under reduced pressure to afford ethyl 2-((2-propylimidazo[1,2-a]pyridin-3-yl)amino)acetate, **4y** (22 mg, 0.084 mmol, 8 % yield) as a pale yellow oil.

5y (4 mg, 1 % yield) was also isolated as a yellow-brown oil from the same purification. A mechanism for its formation is postulated below. The relative stereochemistry of the by-product was not determined.

Ethyl 2-((2-(4-hydroxyheptan-3-yl)imidazo[1,2-a]pyridin-3-yl)amino)acetate 5y



5y

IR ν_{max} (cm^{-1}): 3315, 2959, 2935, 2877, 1741, 1202.

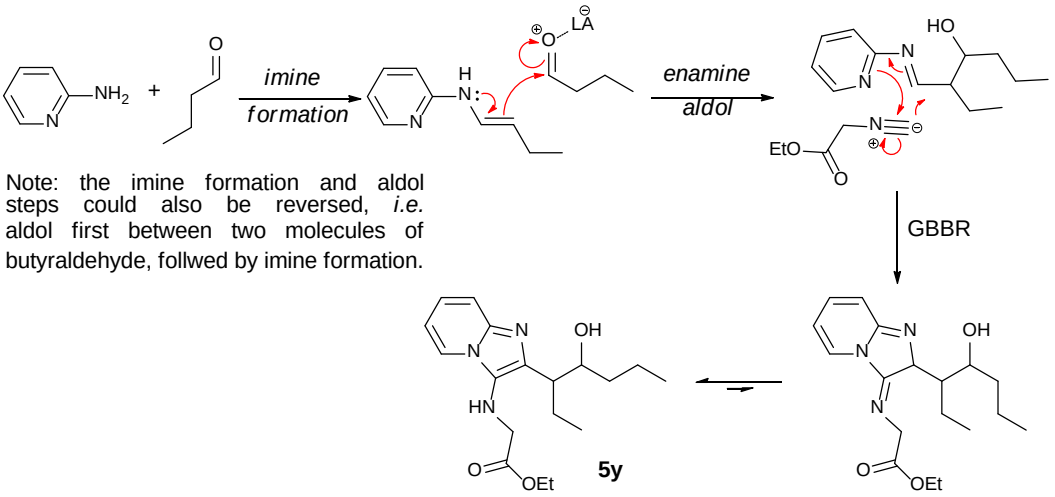
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (app. dt, *J* = 6.8, $^{4}J_{HH}$ = 1.1 Hz, 1H, CH^{1}), 7.45 (app. dt, *J* = 8.9, $^{4}J_{HH}$ = 1.1 Hz, 1H, CH^{4}), 7.13 (ddd, *J* = 8.9, 6.8, $^{4}J_{HH}$ = 1.1 Hz, 1H, CH^{3}), 6.80 (td, *J* = 6.8, $^{4}J_{HH}$ = 1.1 Hz, 1H, CH^{2}), 4.25 (q, *J* = 7.2 Hz, 2H, CH_2^{15}), 3.93-3.83 (m, 1H, CH^{8}), 3.76 (dd, *J* = 5.5, 3.7 Hz, 2H, CH_2^{14}), 3.58 (t, *J* = 5.5 Hz, 1H, NH^{13}), 2.84-2.80 (m, 1H, CH^{5}), 1.96-1.87 (m, 2H, CH_2^{6}), 1.52-1.45 (m, 1H, CH_2^{11} (1H)), 1.39-1.33 (m, 1H, CH_2^{11} (1H)), 1.29 (t, *J* = 7.2 Hz, 3H, CH_3^{16}), 1.25-1.14 (m, 2H, CH_2^{10}), 0.86 (app. t, *J* = 7.3 Hz, 6H, CH_3^{7} + CH_3^{12}).

^{13}C NMR: ($CDCl_3$): δ 171.9 (C^{4a}), 141.5 (C^{1a}), 139.7 (C^{3a}), 126.6 (C^{2a}), 123.8 ($C^{3}H$), 122.5 ($C^{1}H$), 117.2 ($C^{4}H$), 111.6 ($C^{2}H$), 74.0 ($C^{8}H$), 61.4 ($C^{15}H_2$), 50.4 ($C^{14}H_2$), 43.4 ($C^{5}H$), 39.2 ($C^{10}H_2$), 26.1 ($C^{6}H_2$), 19.4 ($C^{11}H_2$), 14.1 ($C^{12}H_3$), 13.2 ($C^{16}H_3$), 12.5 ($C^{7}H_3$).

LCMS (High pH, UV, ESI): R_t = 1.06 min, $[M+H]^+$ 334.2 m/z.

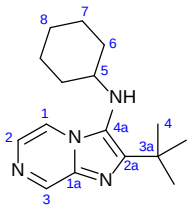
HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{18}H_{28}N_3O_3$: 334.2131, found: 334.2129.

Possible mechanism for formation of 5y:



Note: the imine formation and aldol steps could also be reversed, *i.e.* aldol first between two molecules of butyraldehyde, follwed by imine formation.

2-(*tert*-Butyl)-*N*-cyclohexylimidazo[1,2-a]pyrazin-3-amine 4z



4z

The reaction was performed according to **General Procedure D**, using aminopyazine **1k** (95 mg, 1.00 mmol), pivaldehyde **2l** (217 µL, 2.00 mmol) and cyclohexylisocyanide **3i** (249 µL, 2.00 mmol) as the reaction components. Following the allotted reaction time, a 10 µL aliquot of the reaction mixture was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 61 % of the starting material had been consumed in the reaction. The reaction mixture was concentrated *in vacuo*, and the desired product was purified by flash column chromatography using an 80 g RediSep silica cartridge, with an elution gradient of 20 % ethyl acetate in cyclohexane to 50 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent removed *in vacuo* to afford ethyl 2-((2-propylimidazo[1,2-a]pyridin-3-yl)amino)acetate **4z** (139 mg, 0.510 mmol, 51 % yield) as an off-white flaky solid.

mp: 126-127 °C.

IR ν_{max} (cm^{-1}): 3313, 3260, 2925, 2853, 1528, 1344, 801.

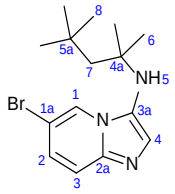
^{1}H NMR (400 MHz, CD_3OD): δ 8.74 (d, *J* = 1.0 Hz, 1H, CH^3), 8.26 (dd, *J* = 4.5, $^5J_{HH}$ = 1.5 Hz, 1H, CH^1), 7.79 (d, *J* = 4.5 Hz, 1H, CH^2), 3.03 (tt, *J* = 10.5, 3.5 Hz, 1H, CH^5), 1.82-1.72 (m, 4H, $CH_2{}^6$), 1.67-1.60 (m, 1H, 1 × $CH_2{}^8$), 1.49 (s, 9H, $CH_3{}^4$), 1.38-1.21 (m, 5H, 1 × $CH_2{}^8$, $CH_2{}^7$).

^{13}C NMR: (101 MHz, CD_3OD): δ 150.8 (C^{1a}), 142.2 (C^3H), 136.9 (C^{4a}), 129.1 (C^2H), 127.7 (C^{2a}), 118.1 (C^1H), 59.5 (C^5H), 35.2 (C^7H_2), 34.5 (C^6H_2), 30.8 (C^4H_3), 26.9 (C^{3a}), 26.2 (C^8H_2).

LCMS (High pH, UV, ESI): R_t = 1.20 min, $[M+H]^+$ 273.3 m/z.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{16}H_{25}N_4$: 273.2079, found: 273.2082.

6-Bromo-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-a]pyridin-3-amine 4aa



4aa

The scale-up synthesis of **4aa** was performed using the bespoke flow reactor setup outlined in Section 1.10. A stock solution of 5-bromo-2-aminopyridine **1n** (3.46 g, 20.0 mmol), and 1,1,3,3-tetramethylbutylisocyanide **3d** (7.01 mL, 40.0 mmol) was prepared in ethanol (100 mL total solution volume). Then, a solution of formaldehyde **2h** (1.67 mL, 37 % wt. solution in H_2O, 22.4 mmol), and HCl (1.60 mL, 1.25 M solution in ethanol, 2.00 mmol) was prepared in ethanol (100 mL total solution volume). The bespoke flow reactor (with 2 × 10 mL loop reactors attached) was heated to 130 °C whilst pumping clean ethanol through the system at a flow rate of 0.2 mL/min/line. Once at temperature, each of the two input lines was placed into one of the two stock solutions, and the reagents were pumped at 0.2 mL/min/line. The reaction mixture was pumped to waste for 12.5 min to account for the dead volume (5 mL) in the reactor. The reaction solution was then collected for 400 min, before the input lines were changed to solvent, and the remainder of the reaction mixture was collected for 74.25 min to account for both dilution and dead volume in the reactor (189.7 mL collected in total), after which time the flow reactor was cooled and turned off. This equates to a total of 90% of the volume of the stock solution being used in the reactor. Therefore, assuming an equal distribution or the reactant materials within the solution, 18 mmol of the amidine reagent (1 eq.) was utilised during the reaction. Following completion of the reaction, a 10 µL aliquot of the crude product solution was taken and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed that 86% of the starting material had been consumed in the reaction. The reaction solution was concentrated *in vacuo*, and the desired product was purified by flash column chromatography using a 330 g RediSep silica cartridge, with an elution gradient of 40 % TBME in cyclohexane to 60 % TBME in cyclohexane. The product containing fractions were combined, and the solvent removed *in vacuo*. The product was dissolved in acetonitrile (~20 mL) and recrystallised following the addition of water (~ 2 mL). Following filtration, 6-bromo-*N*-(2,4,4-trimethylpentan-2-yl) imidazo[1,2-a]pyridin-3-amine **4aa** (4.09 g, 12.6 mmol, 70 % yield) was isolated as a light brown powder.

Note: The reaction is not limited by further scalability. The starting materials and product are soluble up to at least 5 times the concentration used (0.5 M), and further modification of the flow equipment is facile for larger scale syntheses.

mp: 67-68 °C.

IR ν_{max} (cm^{-1}): 3324, 2956, 1534, 1322, 1108, 795.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.50-8.48 (m, 1H, CH^{1}), 7.40 (d, *J* = 9.5 Hz, 1H, CH^{3}), 7.14 (dd, *J* = 9.5, $^{4}J_{HH}$ = 1.8 Hz, 1H, CH^{2}), 7.14 (s, 1H, CH^{4}), 4.60 (s, 1H, NH^{5}), 1.64 (s, 2H, $CH_2{}^{7}$), 1.23 (s, 6H, $CH_3{}^{6}$), 1.00 (s, 9H, $CH_3{}^{8}$).

^{13}C NMR (101 MHz, DMSO-*d*$_6$): δ 138.5 (C^{2a}), 129.2 (C^{3a}), 124.5 ($C^{2}H$), 123.8 ($C^{4}H$), 122.8 ($C^{1}H$), 118.0 ($C^{3}H$), 105.1 (C^{1a}), 55.9 (C^{4a}), 53.0 ($C^{7}H_2$), 31.4 (C^{5a}), 31.3 ($C^{8}H_3$), 29.0 ($C^{6}H_3$).

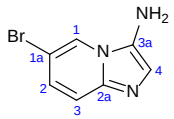
LCMS (High pH, UV, ESI): R_t = 1.39 min, $[M+H]^+$ 324.2 m/z.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_{15}H_{23}{}^{79}BrN_3$: 324.1075, found: 324.1074 . m/z calculated for $[M+H]^+$ $C_{15}H_{23}{}^{81}BrN_3$: 326.1055, found: 326.1076.

Preparation under batch conditions:

The reaction was performed using conditions reported in the patent literature.[5] To a solution of 5-bromo-2-aminopyridine **1n** (3.11 g, 18.0 mmol) and formaldehyde **2h** (1.49 mL, 37 % wt. solution in H_2O, 19.8 mmol) in a mixture of methanol (16.4 mL) and dichloromethane (32.7 mL) was added 1,1,3,3-tetramethylbutylisocyanide **3d** (3.79 mL, 21.6 mmol) and scandium(III)trifluoromethanesulfonate (443 mg, 0.900 mmol). The reaction mixture was stirred under ambient conditions for 20 h. During the course of the reaction, 10 µL aliquots were removed from the reaction mixture at 50 min and 20 h time points, and analysed according to the HPLC method described above (see Section 4.1 Procedure for deriving conversion estimates from HPLC concentration gradients), which showed 65 % consumption of the starting material after 50 min and an 88 % consumption after 20 h. The reaction mixture was concentrated *in vacuo*, and the residue purified by flash column chromatography, using a 330 g RediSep silica cartridge, with an elution gradient of 20 % ethyl acetate in cyclohexane to 40 % ethyl acetate in cyclohexane. The product-containing fractions were combined, and the solvent was removed *in vacuo* to afford 6-bromo-*N*-(2,4,4-trimethylpentan-2-yl) imidazo[1,2-a]pyridin-3-amine **4aa** (3.63 g, 11.2 mmol, 62 % Yield) as a light brown powder.

6-Bromoimidazo[1,2-a]pyridin-3-amine 4ab



4ab

A solution of 6-bromo-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-a]pyridin-3-amine **4aa** (4.00 g, 12.3 mmol) in HCl (50 mL, 6 M in *iso*-propanol, 300 mmol) was stirred at room temperature for 24 h under a nitrogen atmosphere. The reaction mixture was then concentrated *in vacuo*, and the resultant material was dissolved in a mixture of methanol (30 mL) and water (20 mL), passed through an Isolute® 2 g amino propyl frit, and the solvent was removed *in vacuo* to afford 6-bromoimidazo[1,2-a] pyridine-3-amine **4ab** (2.62 g, 12.4 mmol, 100 % yield) as an off-white powder.

mp: 215-216 °C (dec.)

IR ν_{max} (cm^{-1}): 3482, 3410, 2816, 1655, 1510, 827, 772.

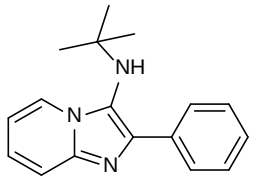
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 9.00 (dd, $^{4}J_{HH}$ = 1.8, $^{5}J_{HH}$ = 1.0 Hz, 1H, CH^{1}), 7.87-7.79 (m, 2H, CH^{2}, CH^{3}), 7.28 (s, 1H, CH^{4}), 4.60 (br. s, 2H, NH_2).

^{13}C NMR (101 MHz, DMSO-*d*$_6$): δ 133.4 (C^{2a}), 133.0 ($C^{2}H$), 132.4 (C^{3a}), 124.4 ($C^{1}H$), 113.2 ($C^{3}H$), 109.3 (C^{1a}), 102.8 ($C^{4}H$).

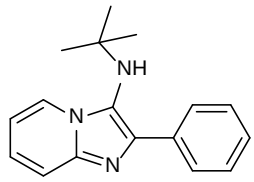
LCMS (High pH, UV, ESI): R_t = 0.62 min, $[M]^-$ 210.0 m/z.

HRMS (TOF ESI, formic acid): m/z calculated for $[M+H]^+$ $C_7H_7{}^{79}BrN_3$: 211.9823, found: 211.9824. m/z calculated for $[M+H]^+$ $C_7H_7{}^{81}BrN_3$: 213.803, found: 213.9806.

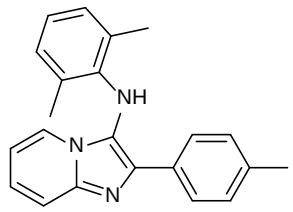
6. ^{1}H and ^{13}C NMR spectra



4a

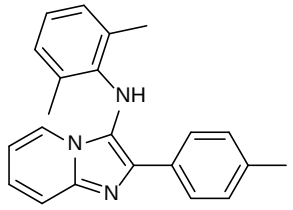


4a

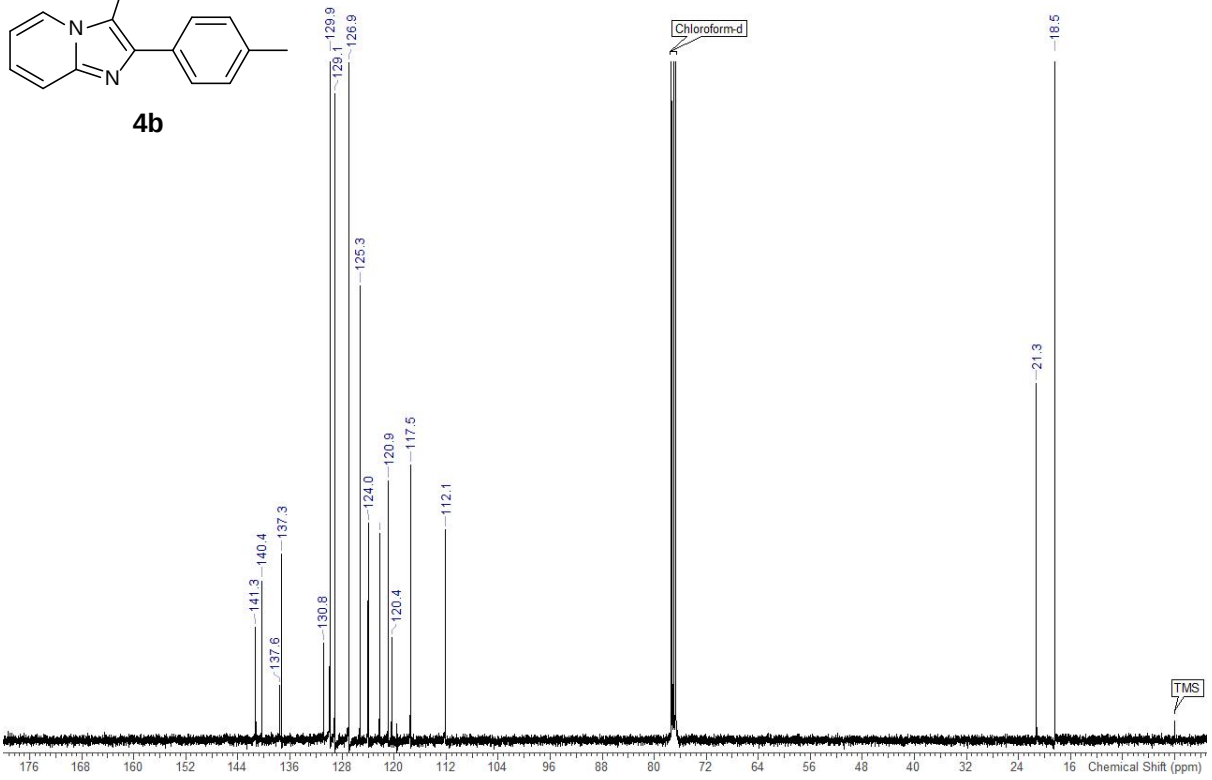

NH
N
N

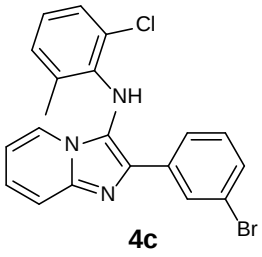
4b

2.0
2.3
Chloroform-d
8.0
8.0
7.6
7.6
7.5
7.2
7.1
7.0
6.8
6.8
6.6
5.4
TMS
0.0
1.99
1.97
2.00
1.02
2.00
1.00
1.00
1.00
3.00
6.00
Chemical Shift (ppm)


NH
N
N

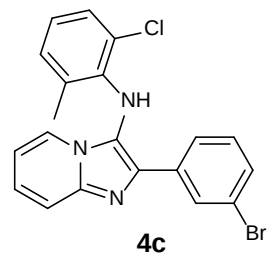
4b


129.9
129.1
126.9
Chloroform-d
18.5
125.3
21.3
120.9
117.5
124.0
112.1
141.3
140.4
137.3
130.8
137.6
120.4
TMS
Chemical Shift (ppm)


Cl
NH
N
N
Br

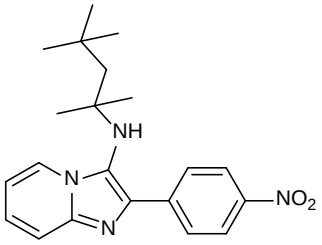
4c

1.6
Chloroform-d
TMS
8.2
8.2
8.0
8.0
7.9
7.8
7.6
7.6
7.4
7.4
7.2
7.2
7.2
7.2
6.8
6.8
6.8
6.8
6.9
6.8
6.1
0.96 1.01 1.01 1.00 1.00 1.00 2.14 3.12
0.99
3.18
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
Chemical Shift (ppm)


Cl
NH
N
N
Br

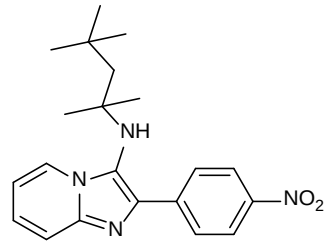
4c

Chloroform-d
127.6
125.7
129.8
130.1
131.2
130.6
121.7
138.5
122.5
123.1
117.7
112.8
141.7
135.1
120.0
18.2
TMS
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16
Chemical Shift (ppm)


NH
N
N
NO2

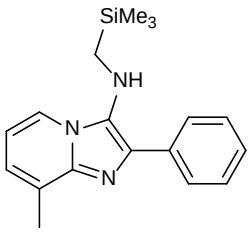
4d

1.1
1.0
1.6
TMS
Chloroform-d
8.3
8.2
8.3
8.2
7.6
7.5
1.98
3.00
0.99
1.01
1.00
0.92
2.00
9.00
6.00
Chemical Shift (ppm)


NH
N
N
NO2

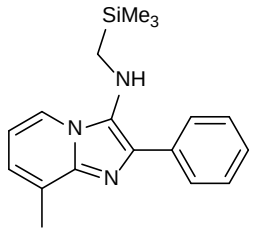
4d

Chloroform-d
123.6
31.9
29.2
128.7
124.9
123.5
117.8
112.0
61.1
57.3
31.8
146.8
142.6
142.3
137.5
TMS
Chemical Shift (ppm)

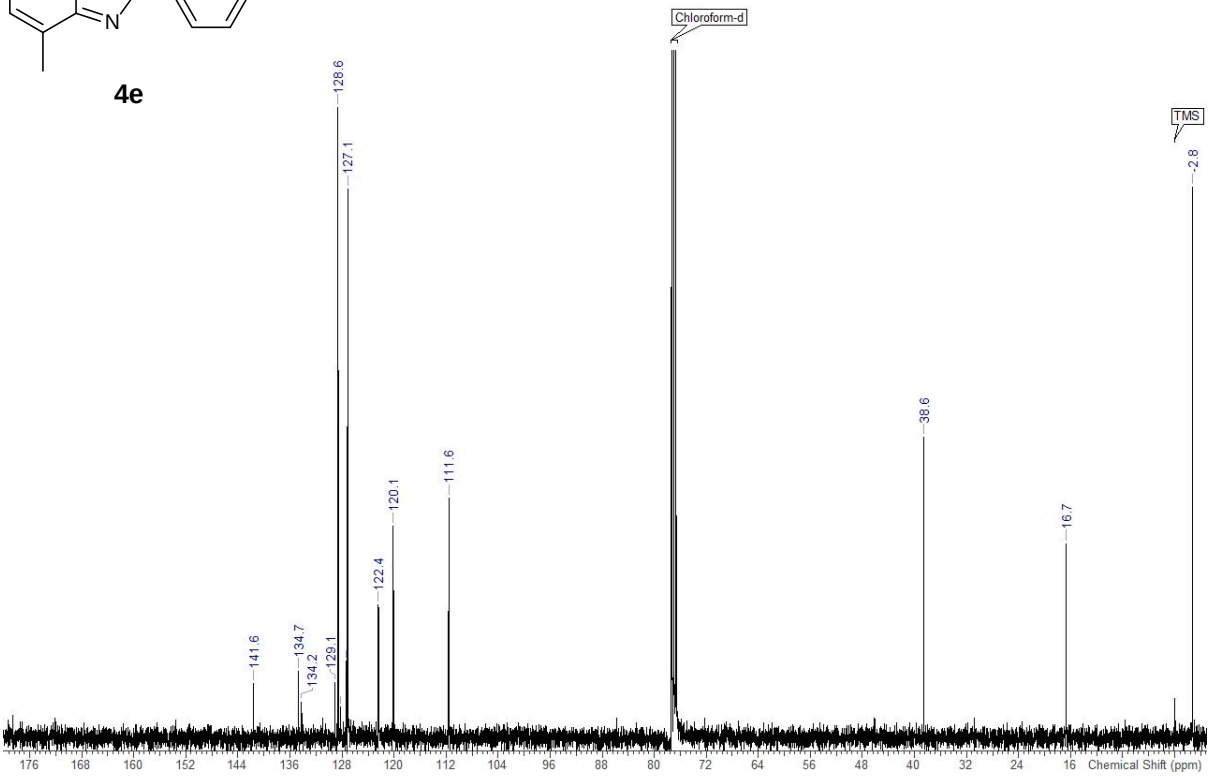

SiMe3
NH
N
N

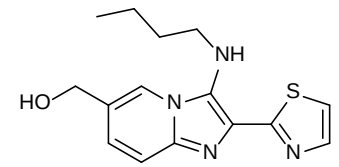
4e

0.2
2.6
2.6
TMS
Chloroform-d
8.0
7.5
1.7
1.7
1.7
1.99 1.00 2.04 0.97 0.99 0.99
3.01 2.00
1.03
8.84
Chemical Shift (ppm)


SiMe3
NH
N
N

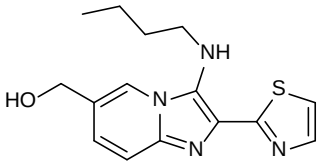
4e


Chloroform-d
128.6
127.1
TMS
2.8
38.6
16.7
120.1
111.6
122.4
141.6
134.7
134.2
129.1
Chemical Shift (ppm)


NH
HO
N
S
N
N

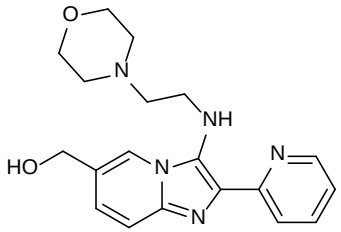
4f

Chloroform-d
TMS
Chemical Shift (ppm)

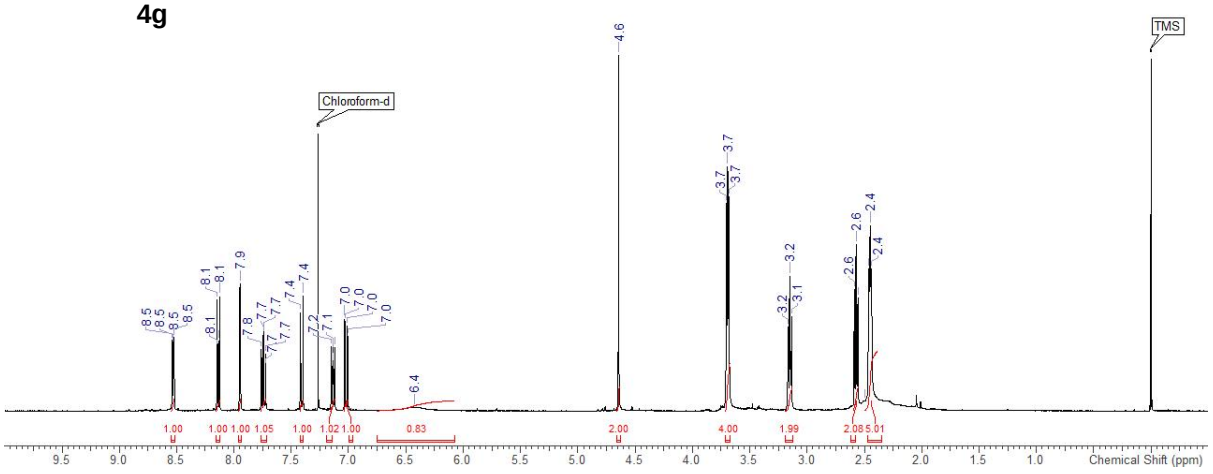

NH
HO
N
S
N
N

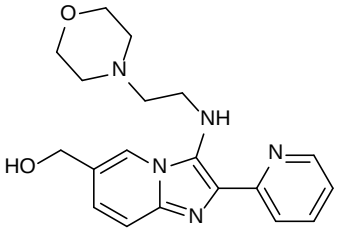
4f

Chloroform-d
TMS
Chemical Shift (ppm)


O
N
NH
HO
N
N
N

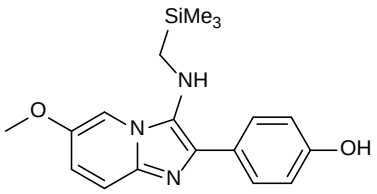
4g


Chloroform-d
TMS
Chemical Shift (ppm)


O
N
NH
HO
N
N
N

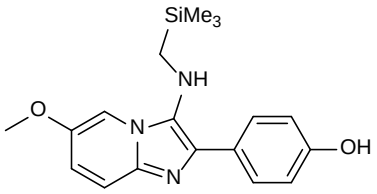
4g

Chloroform-d
TMS
Chemical Shift (ppm)


SiMe3
NH
O
N
N
OH

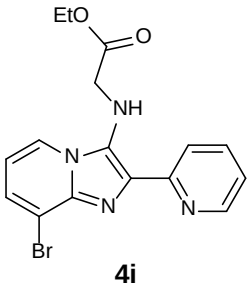
4h

Water
0.1
3.8
DMSO-d6
7.9
7.9
6.8
6.8
7.7
7.4
7.4
6.9
4.3
4.3
2.4
2.4
0.99
1.97
1.00
1.00
1.00
2.00
1.00
3.00
1.96
8.96
Chemical Shift (ppm)


SiMe3
NH
O
N
N
OH

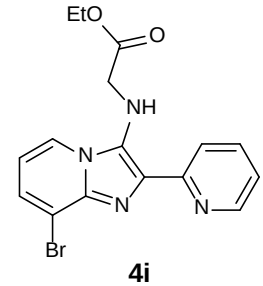
4h

DMSO-d6
115.0
127.6
2.5
55.9
117.7
104.4
128.6
156.3
147.9
137.1
134.9
125.9
37.3
Chemical Shift (ppm)


EtO
O
NH
N
N
N
Br

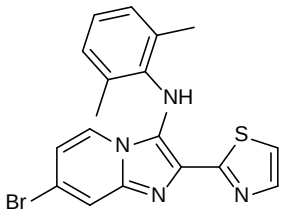
4i

Chloroform-d
TMS
Water
Chemical Shift (ppm)

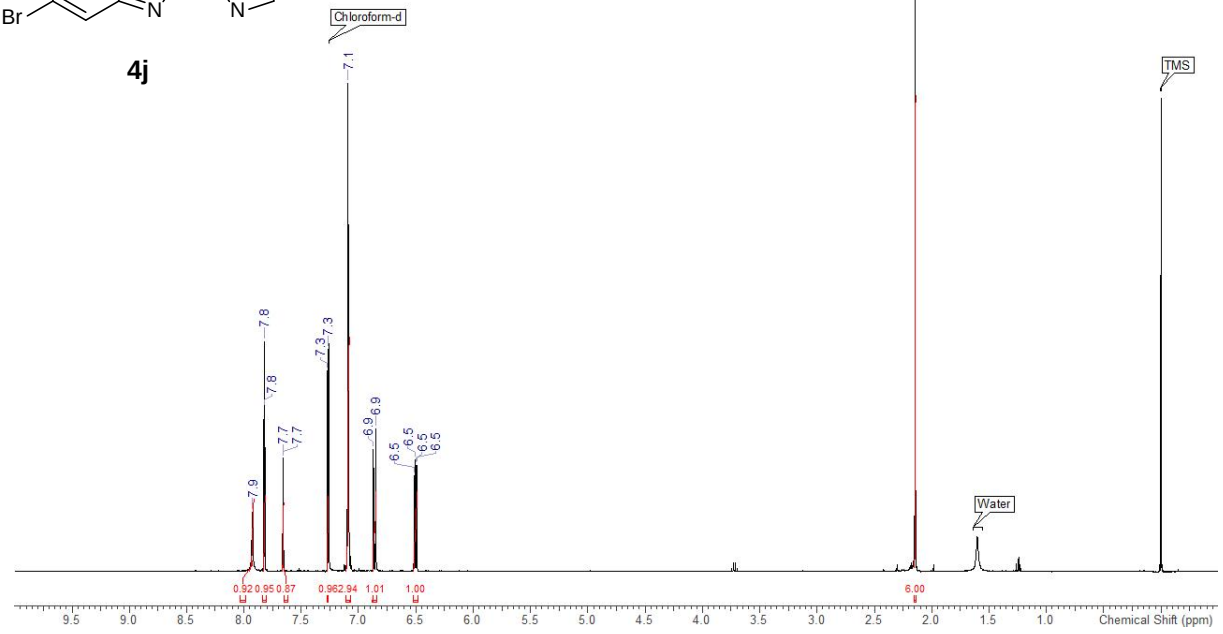

EtO
O
NH
N
N
N
Br

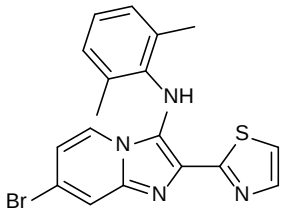
4i

Chloroform-d
TMS
Chemical Shift (ppm)


NH
N
S
N
N
Br

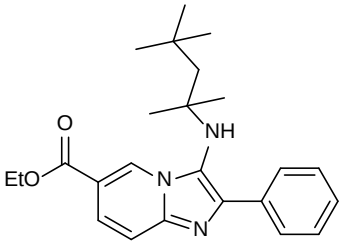
4j


Chloroform-d
TMS
Water
7.9
7.8
7.8
7.7
7.7
7.3
7.3
7.1
6.9
6.9
6.5
6.5
6.5
2.1
0.92 0.95 0.87 0.96 2.94 1.01 1.00 6.00
Chemical Shift (ppm)


NH
N
S
N
N
Br

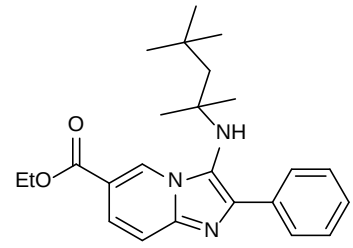
4j

Chloroform-d
77.3
77.0
76.7
164.3
143.0
139.6
136.7
135.3
129.6
129.0
126.3
122.5
120.1
116.9
116.0
18.7
TMS
Chemical Shift (ppm)


O
NH
EtO
N
N

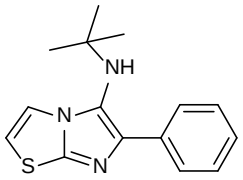
4k

Water
DMSO-d6
1.0
0.9
1.4
1.6
1.4
1.3
4.4
4.4
4.7
8.1
8.1
7.6
7.6
7.6
7.4
7.3
7.3
7.3
9.1
DMSO-d6
DMSO-d6
TMS
0.98
2.00
0.99
1.00
2.00
1.02
0.98
2.05
1.99
3.00
9.00
6.00
Chemical Shift (ppm)


O
NH
EtO
N
N

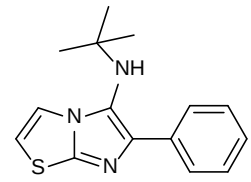
4k

DMSO-d6
31.6
31.3
28.8
30.3
14.1
178.8
164.6
141.4
140.1
134.8
128.0
127.9
128.1
127.4
124.9
122.8
119.1
116.3
114.5
60.9
59.9
56.1
Chemical Shift (ppm)


NH
N
S
N

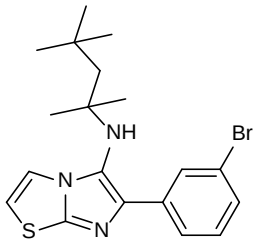
4l

1.1
Chloroform-d
7.4
6.7
6.7
7.9
7.9
7.9
7.4
7.3
7.4
7.2
7.2
7.2
7.4
7.4
7.9
3.1
Water
TMS
2.02
2.01
1.02
1.19
1.01
0.99
9.05
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)


NH
N
S
N

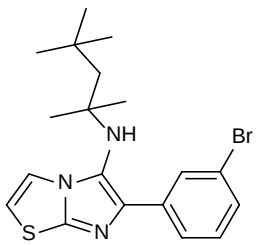
4l

128.2
127.2
Chloroform-d
30.2
126.7
117.8
111.4
55.8
145.5
140.2
135.3
125.5
TMS
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)


NH
Br
N
S
N

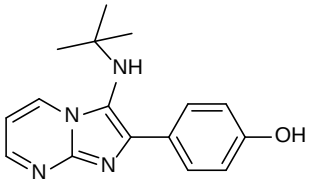
4m

1.1
1.0
1.6
7.4
Chloroform-d
TMS
6.8
6.7
7.3
7.2
8.1
7.4
7.8
7.8
7.8
7.8
0.99
1.00
2.01
1.41
1.00
2.00
8.73
5.98
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

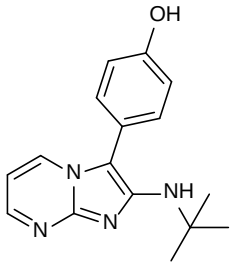

NH
Br
N
S
N

4m

Chloroform-d
31.9
29.2
31.8
130.3
125.8
129.6
111.8
117.8
57.0
60.1
145.8
139.0
137.5
125.6
122.3
TMS
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)

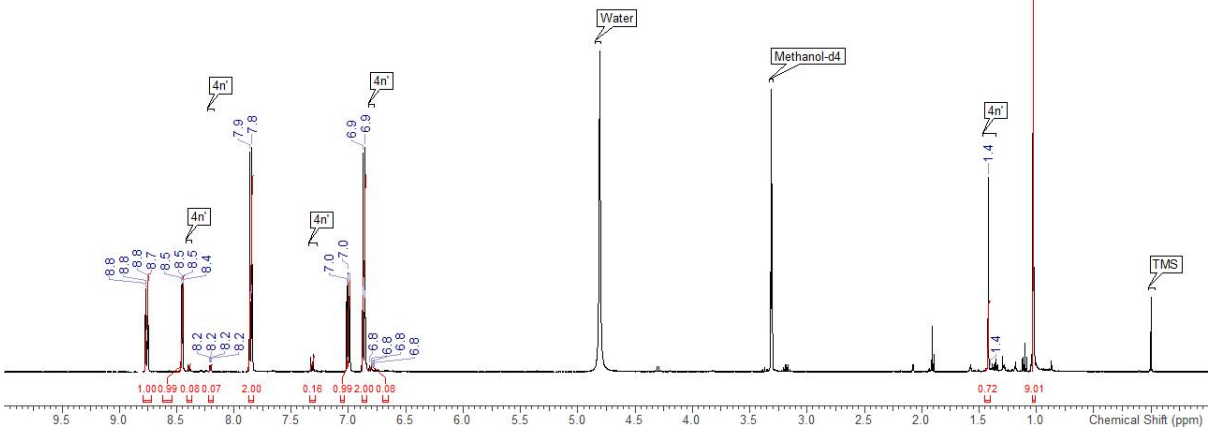


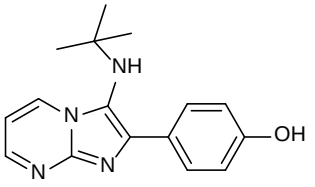
4n



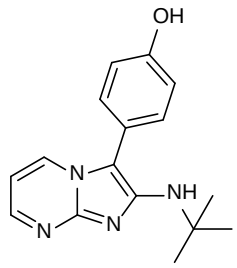
4n'

c. **8 % by NMR analysis**



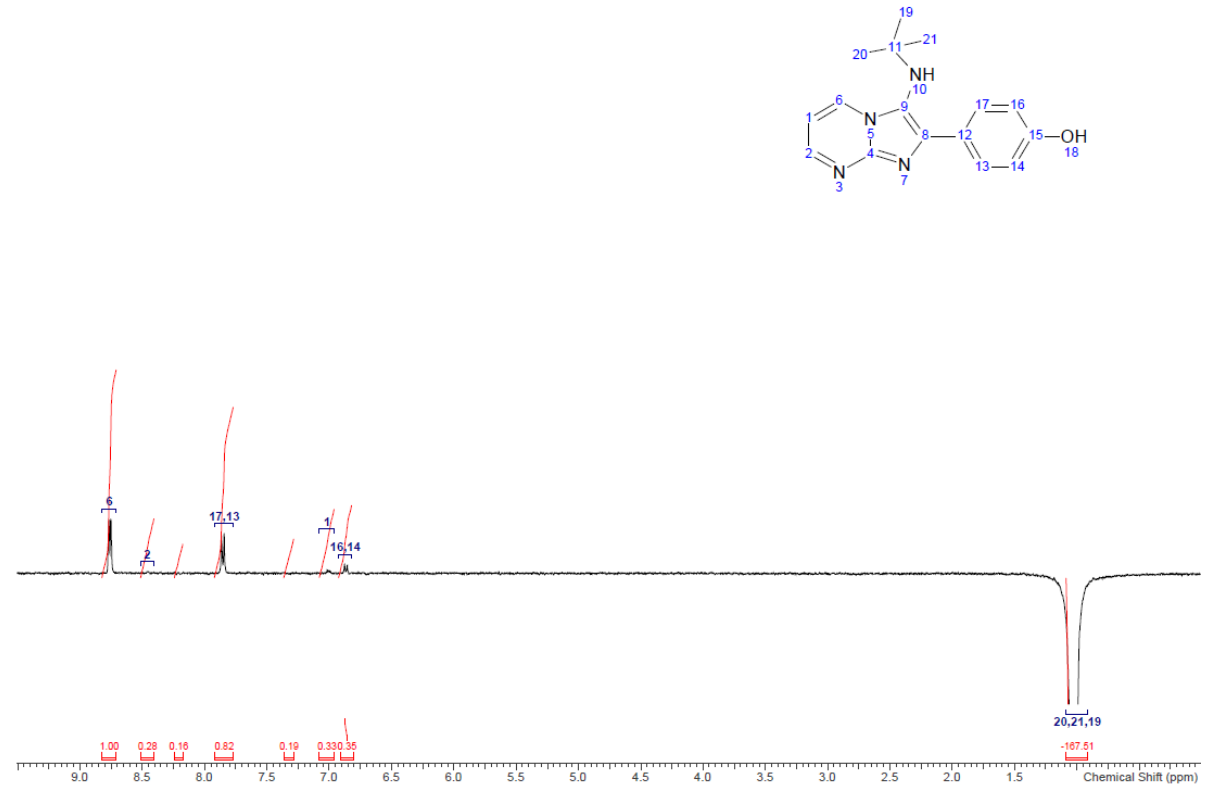


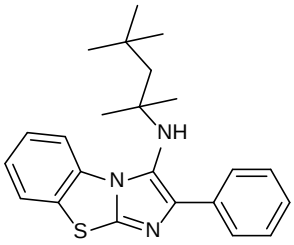
4n



4n'

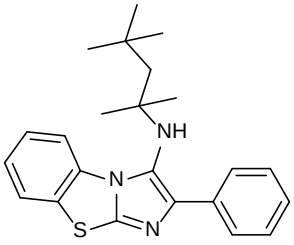
c. **8 % by NMR analysis**


19
20
11
21
NH
10
6
9
1
N
5
17
16
8
12
15
OH
18
2
4
N
N
13
14
3
7
6
2
17,13
1
16,14
20,21,19
1.00
0.28
0.16
0.82
0.19
0.33
0.35
-167.51
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)


NH
N
S
N

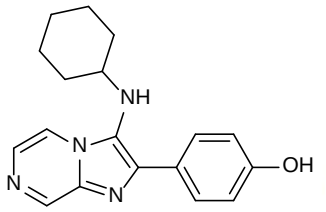
4o

1.0
0.9
Water
DMSO-d6
DMSO-d6
DMSO-d6
7.9
7.9
7.9
7.4
7.4
7.4
1.00
3.02
1.03
3.02
1.00
1.00
2.00
6.00
9.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

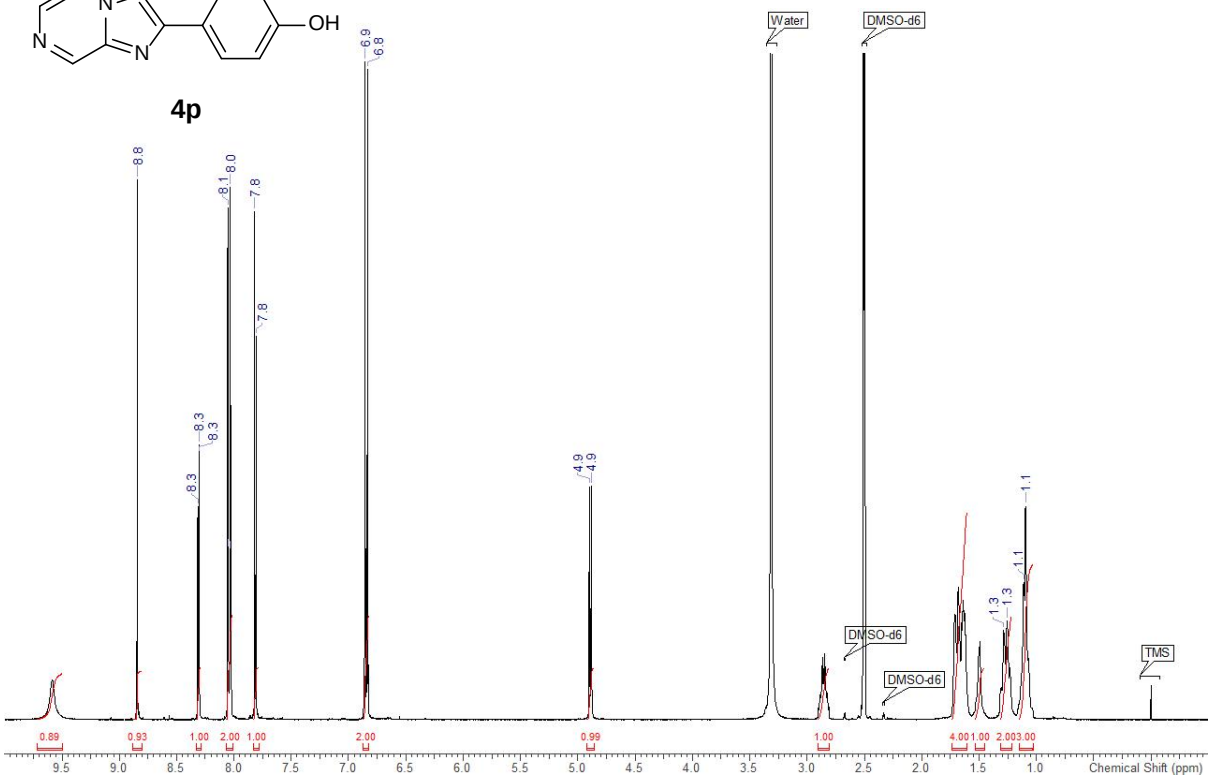

NH
N
S
N

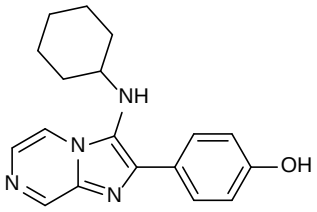
4o

DMSO-d6
31.4
28.0
30.9
59.8
56.0
127.8
127.7
135.3
133.1
129.1
126.6
125.6
124.6
124.4
114.5
142.6
140.6
Chemical Shift (ppm)


NH
N
N
N
OH

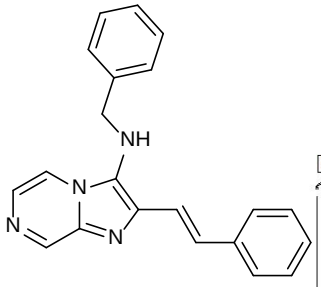
4p


Water
DMSO-d6
DMSO-d6
DMSO-d6
TMS
8.8
8.1
8.0
7.8
7.8
8.3
8.3
8.3
6.9
6.8
4.9
4.9
1.3
1.3
1.1
1.1
0.89
0.93
1.00
2.00
1.00
2.00
0.99
1.00
4.00
1.00
2.00
3.00
Chemical Shift (ppm)

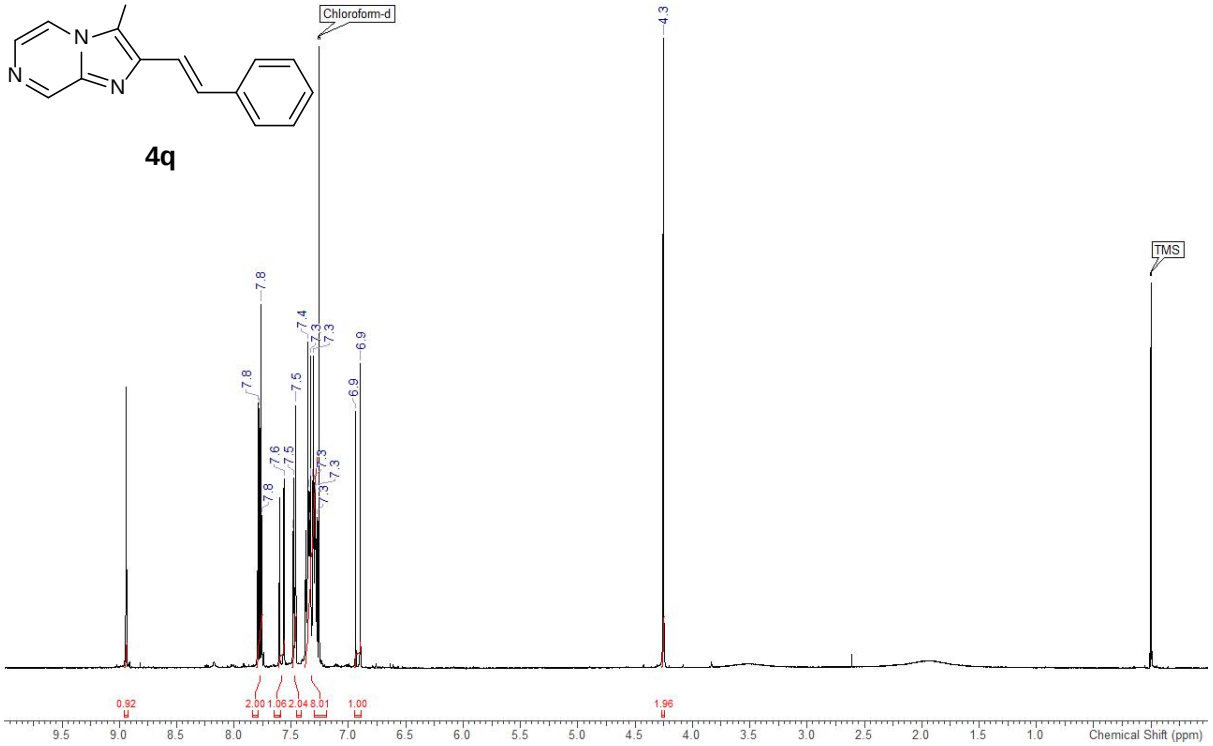

NH
N
N
N
OH

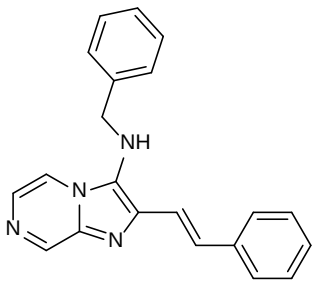
4p

DMSO-d6
157.7
142.3
137.8
136.2
128.8
128.7
126.6
125.2
116.6
115.7
56.7
34.1
25.8
25.0
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 Chemical Shift (ppm)


NH
N
N
N

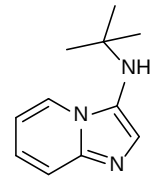
4q


Chloroform-d
4.3
TMS
7.8
7.8
7.8
7.6
7.5
7.5
7.4
7.3
7.3
7.3
7.3
7.3
6.9
6.9
0.92
2.00
1.06
2.04
8.01
1.00
1.96
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 Chemical Shift (ppm)


NH
N
N
N

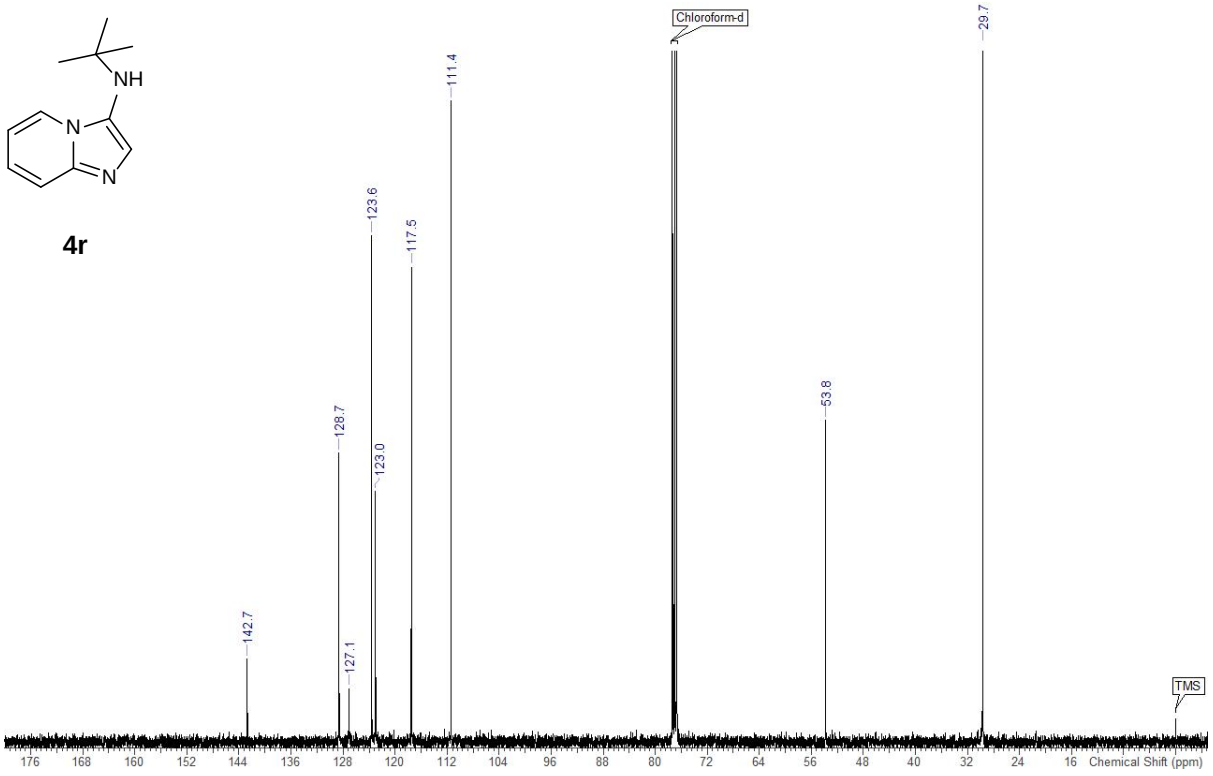
4q

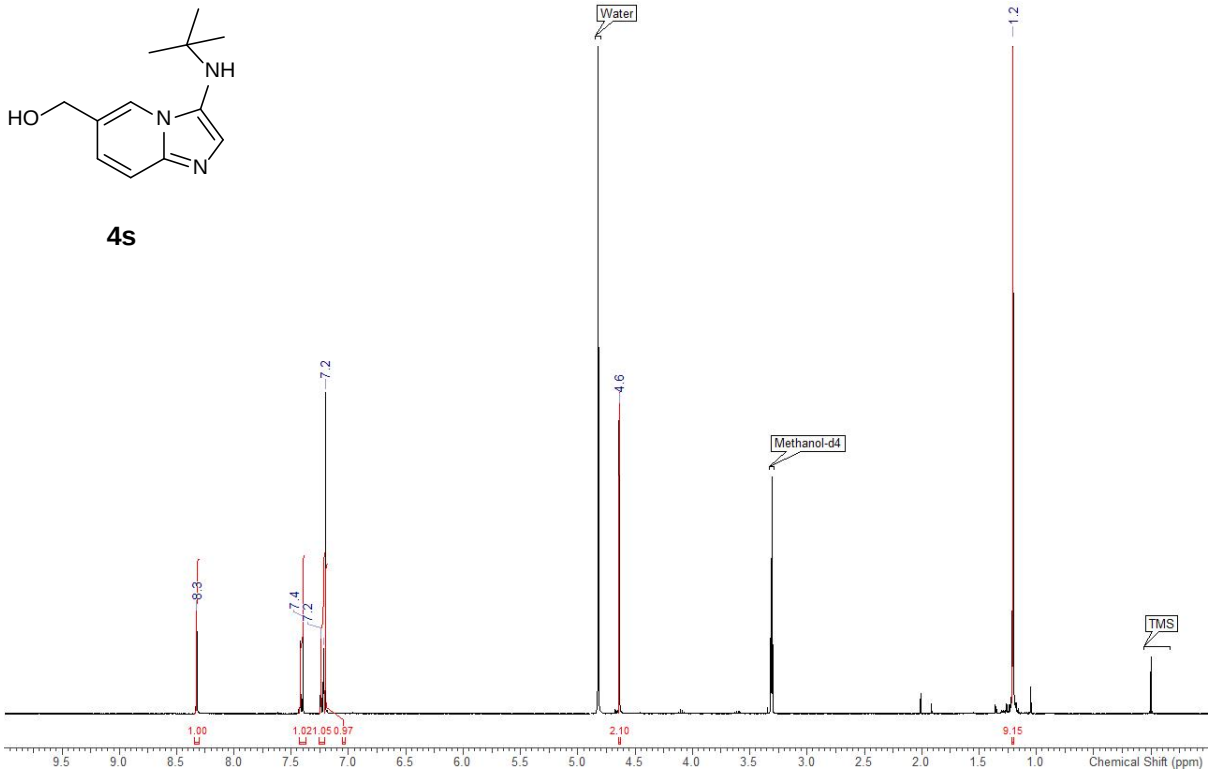
Chloroform-d
143.0
138.8
136.9
131.8
128.9
128.7
128.3
126.8
117.2
115.1
53.2
TMS
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 Chemical Shift (ppm)

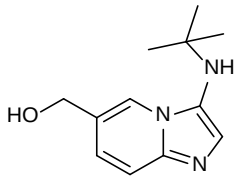

NH
N
N

4r

1.2
Chloroform-d
7.3
6.8
TMS
1.00
1.00
0.97
1.00
0.99
1.04
9.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 Chemical Shift (ppm)

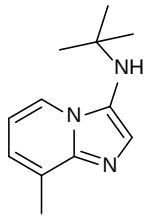

NH
N
N
4r
Chloroform-d
29.7
111.4
123.6
117.5
128.7
123.0
53.8
142.7
127.1
TMS
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 Chemical Shift (ppm)


NH
HO
N
N
4s
Water
1.2
7.2
4.6
Methanol-d4
8.3
7.4
7.2
TMS
1.00
1.02
1.05
0.97
2.10
9.15
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 Chemical Shift (ppm)


NH
HO
N
N

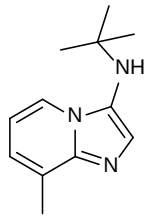
4s

Methanol-d4
29.8
62.7
54.4
126.1
117.1
127.6
127.3
122.1
143.1
129.9
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 Chemical Shift (ppm)

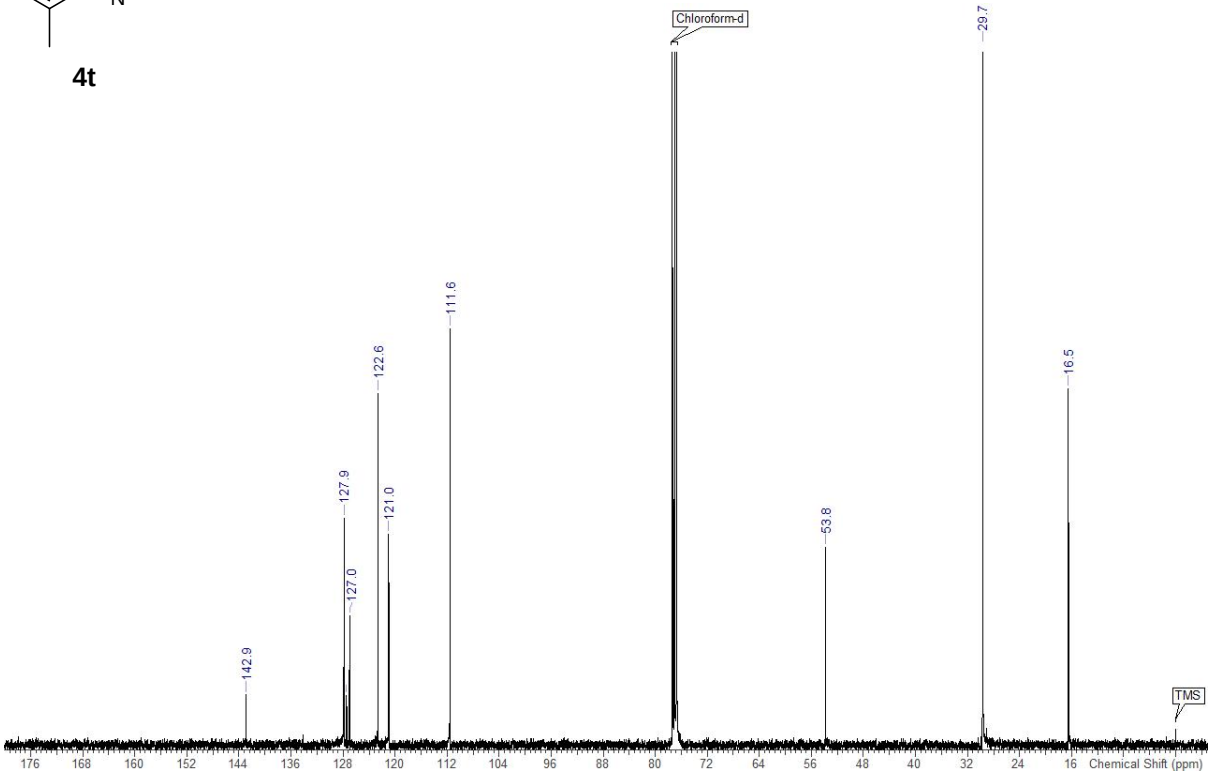

NH
N
N

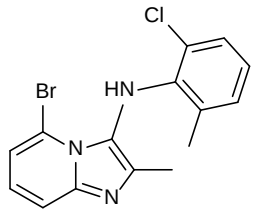
4t

2.6
1.2
TMS
0.0
Chloroform-d
1.00 0.97 1.00 1.00 1.00 3.02 9.06
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 Chemical Shift (ppm)


NH
N
N

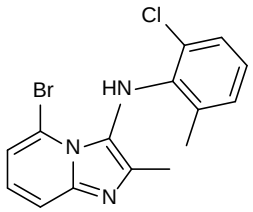
4t


Chloroform-d
29.7
111.6
122.6
16.5
127.9
121.0
53.8
127.0
142.9
TMS
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 Chemical Shift (ppm)


Cl
Br
HN
N
N

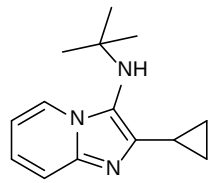
4u

Water
2.1
2.1
1.7
Chloroform-d
TMS
5.9
1.00 1.03 2.00 1.04 1.05
0.99
3.00
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 Chemical Shift (ppm)


Cl
Br
HN
N
N

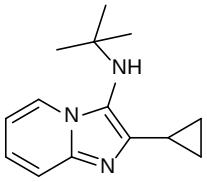
4u

Chlorofom-d
TMS
143.7
140.2
139.8
131.0
127.6
126.8
124.4
122.6
120.7
118.6
116.3
112.1
18.7
12.8
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 Chemical Shift (ppm)


NH
N
N

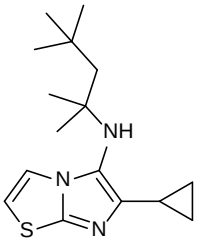
4v

Water
Methanol-d4
TMS
8.3
7.3
7.2
6.9
2.2
1.2
1.0
1.0
1.0
1.0
1.00
0.97
1.02
1.01
1.00
8.99
4.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 Chemical Shift (ppm)


NH
N
N

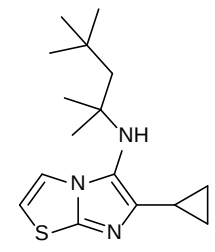
4v

Chloroform-d
30.6
8.7
116.0
125.8
112.6
124.6
56.5
9.6
142.6
142.2
125.9
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 Chemical Shift (ppm)


NH
N
S
N

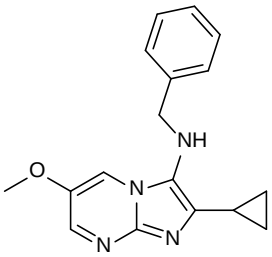
4w

METHANOL-d4
METHANOL-d4
1.2
1.1
1.7
0.8
0.8
0.8
0.9
7.5
7.5
6.9
6.9
2.0
2.0
2.0
2.0
2.0
TMS
1.00
0.99
1.01
2.00
6.01
9.04
4.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 Chemical Shift (ppm)


NH
N
S
N

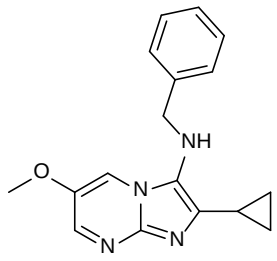
4w

Methanol-d4
32.4
29.6
7.9
9.9
57.2
60.1
112.0
119.6
127.3
143.2
146.0
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 Chemical Shift (ppm)


NH
O
N
N
N

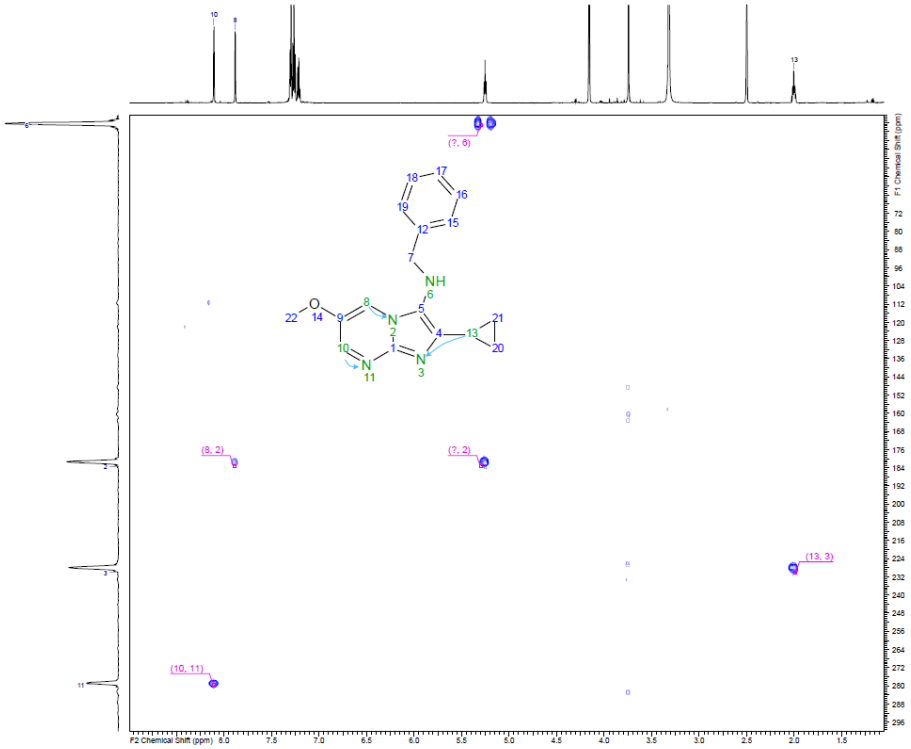
4x

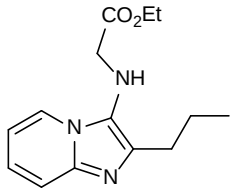
3.7
Water
DMSO-d6
DMSO-d6*
DMSO-d6*
TMS
7.3
7.3
7.2
4.2
4.2
0.8
0.8
0.8
2.0
2.0
2.0
2.0
1.00 1.01 4.22 1.10 0.99 2.00 3.00 1.05 4.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 Chemical Shift (ppm)


NH
O
N
N
N

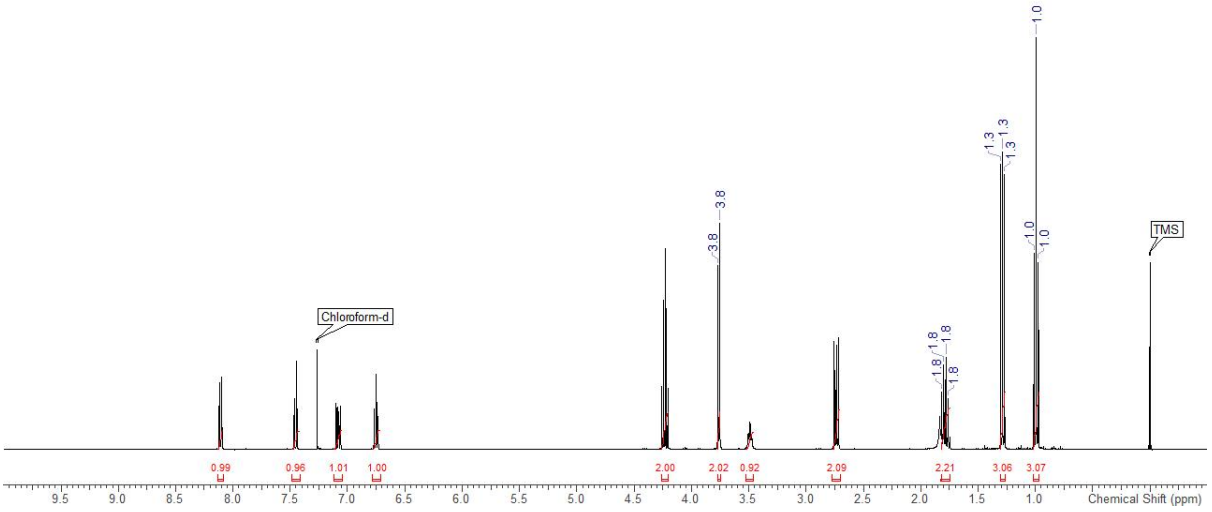
4x

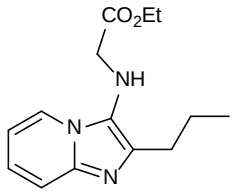
DMSO-d6
128.1
128.3
126.9
125.5
144.3
140.6
140.5
140.3
111.2
56.3
51.9
7.9
8.0
Chemical Shift (ppm)


(7, 6)
(8, 2)
(7, 2)
(13, 3)
(10, 11)
NH
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)


CO2Et
NH
N
N

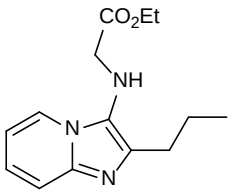
4y


Chloroform-d
TMS
0.99
0.96
1.01
1.00
2.00
2.02
0.92
2.09
2.21
3.06
3.07
Chemical Shift (ppm)

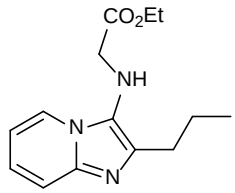

CO2Et
NH
N
N

4y

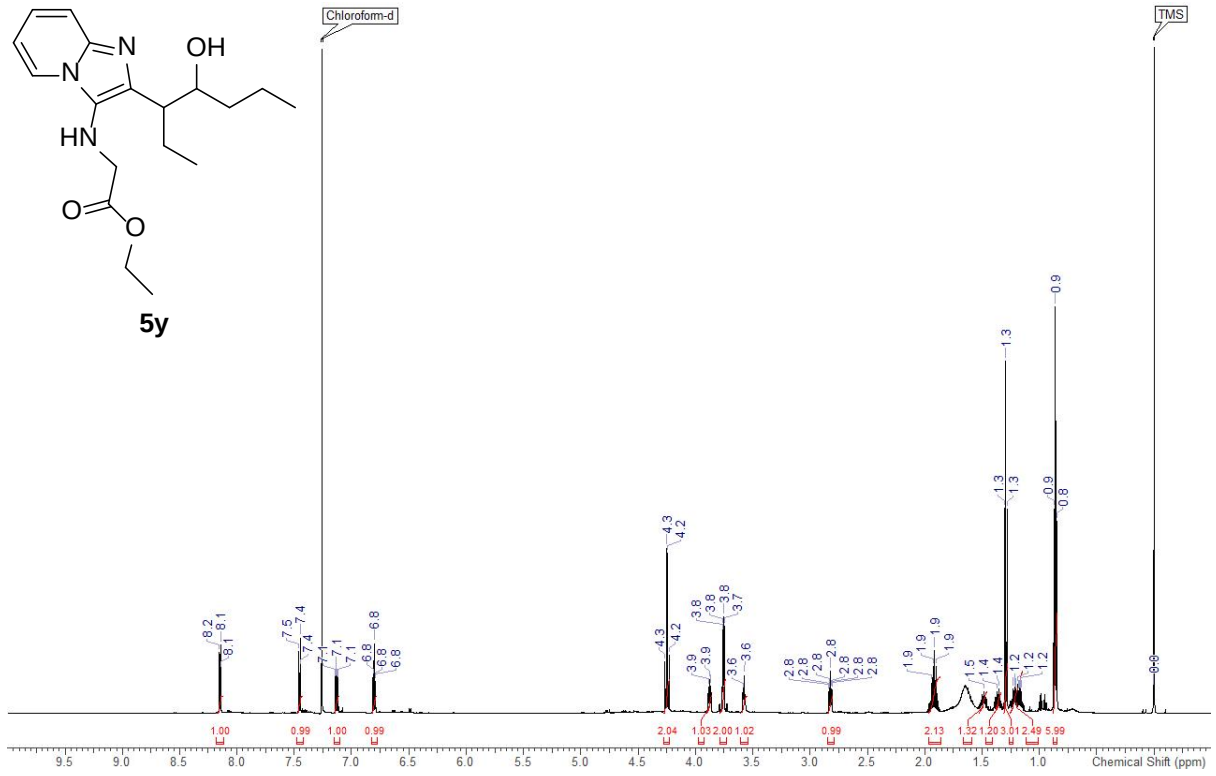
Chloroform-d
TMS
171.9
141.5
139.4
124.9
123.2
122.4
117.0
111.3
61.3
50.3
29.2
22.9
14.2
Chemical Shift (ppm)



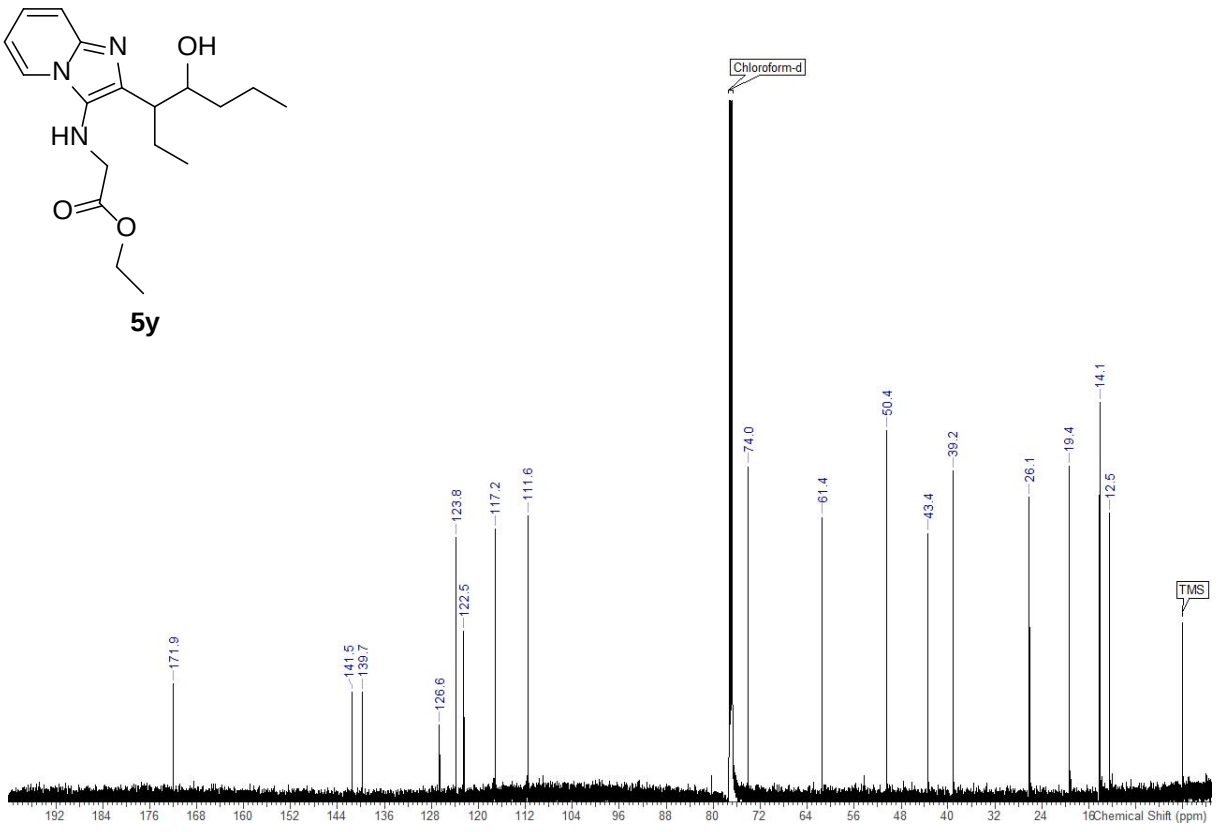
4y (batch)



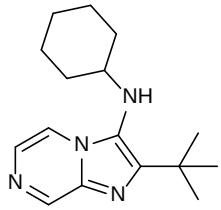
4y (batch)


N
N
OH
HN
O
O
Chloroform-d
TMS
Chemical Shift (ppm)

5y

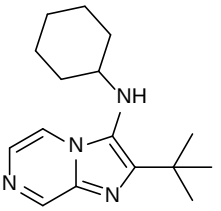

N
N
OH
HN
O
O
Chloroform-d
TMS
Chemical Shift (ppm)

5y


NH
N
N
N

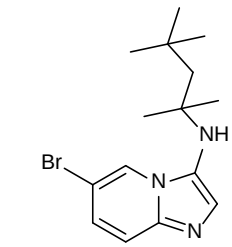
4z

Water
Methanol-d4
TMS
Chemical Shift (ppm)


NH
N
N
N

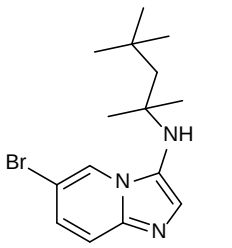
4z

Methanol-d4
Chemical Shift (ppm)


NH
Br
N
N

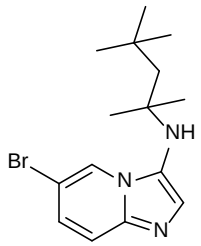
4aa

Water
1.2
1.0
1.6
7.1
8.5
8.5
7.4
7.4
4.6
DMSO-d6
DMSO-d6
DMSO-d6
TMS
1.00
1.00
2.00
1.00
2.00
6.01
9.02
Chemical Shift (ppm)

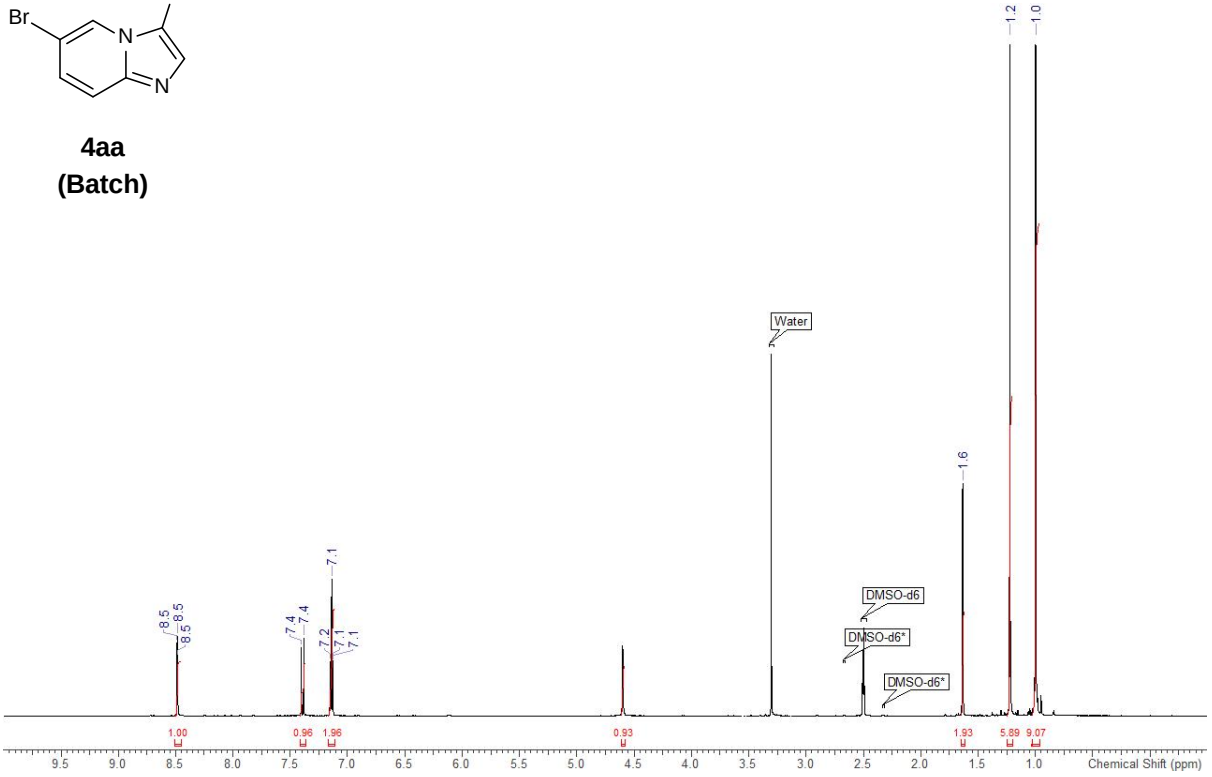

NH
Br
N
N

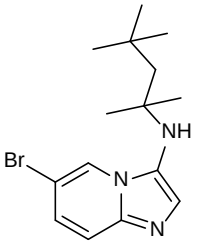
4aa

DMSO-d6
31.4
29.0
31.3
55.9
53.0
124.5
123.8
122.8
118.0
105.1
138.5
129.1
Chemical Shift (ppm)

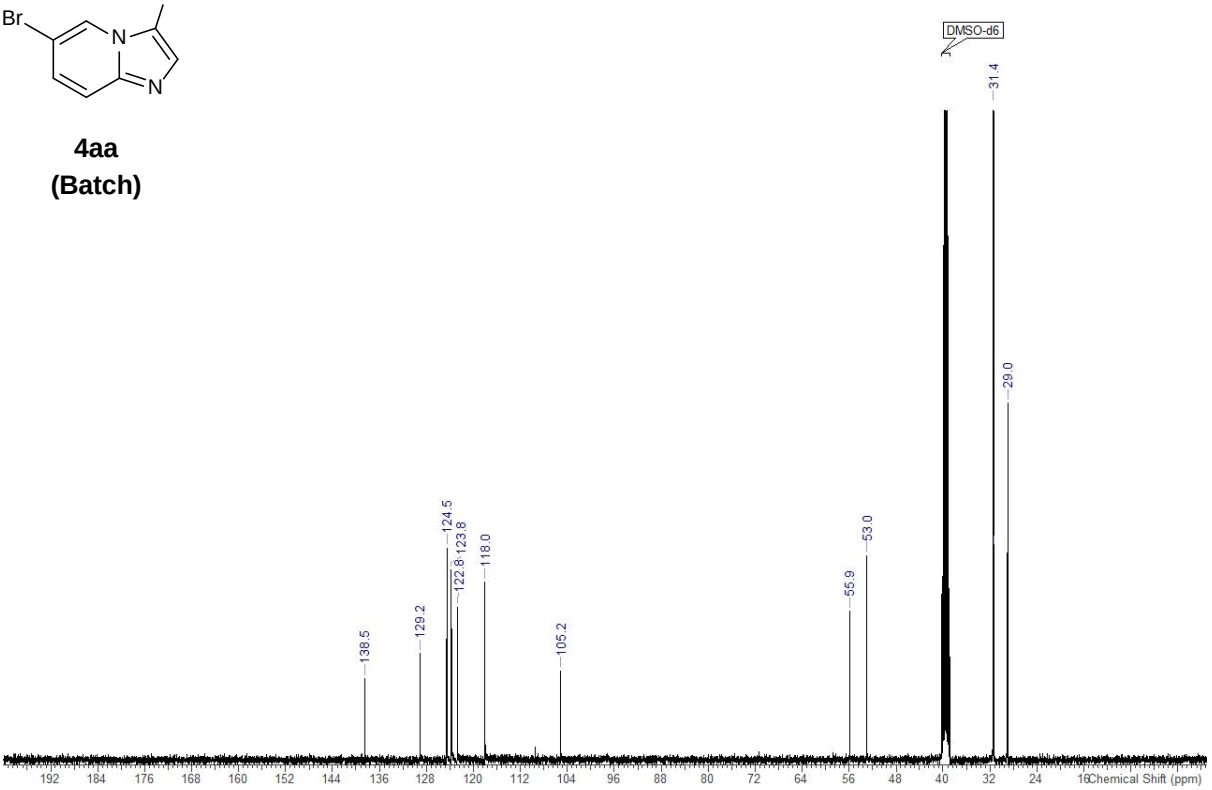


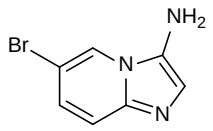
4aa
(Batch)





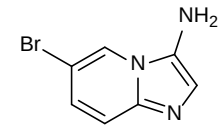
4aa
(Batch)



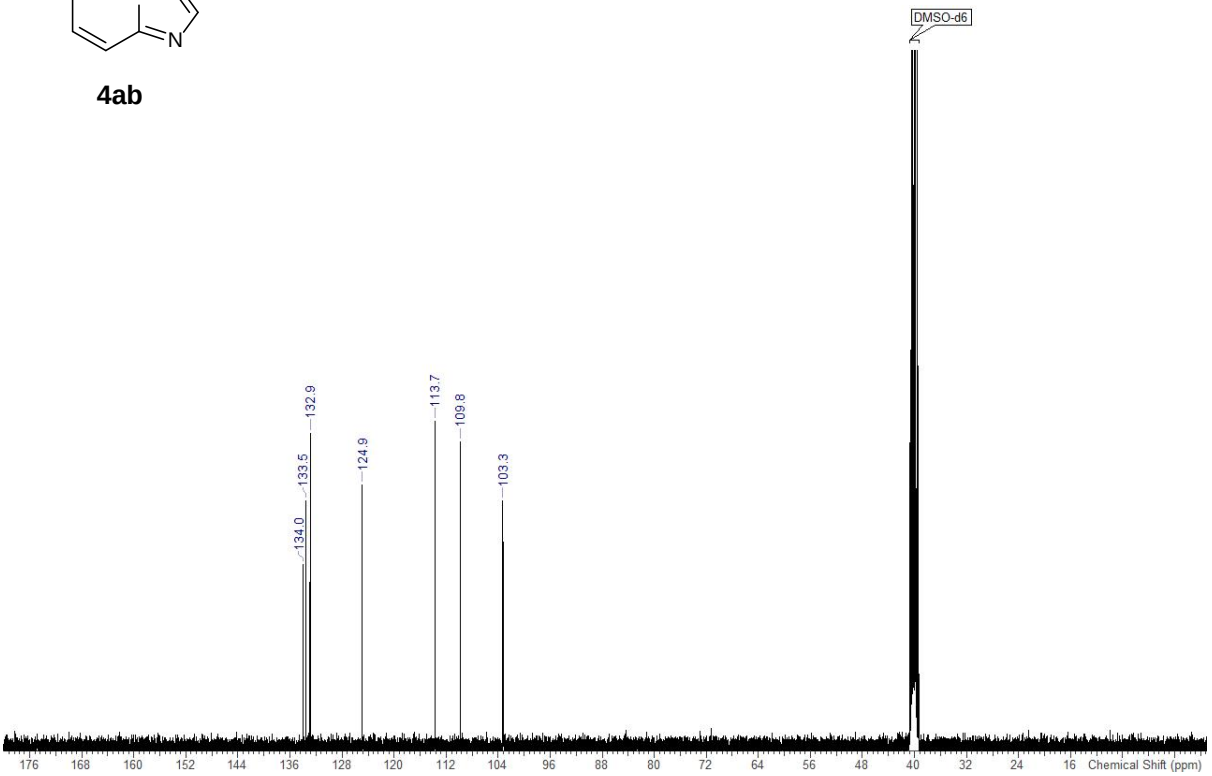

NH2
Br
N
N

4ab

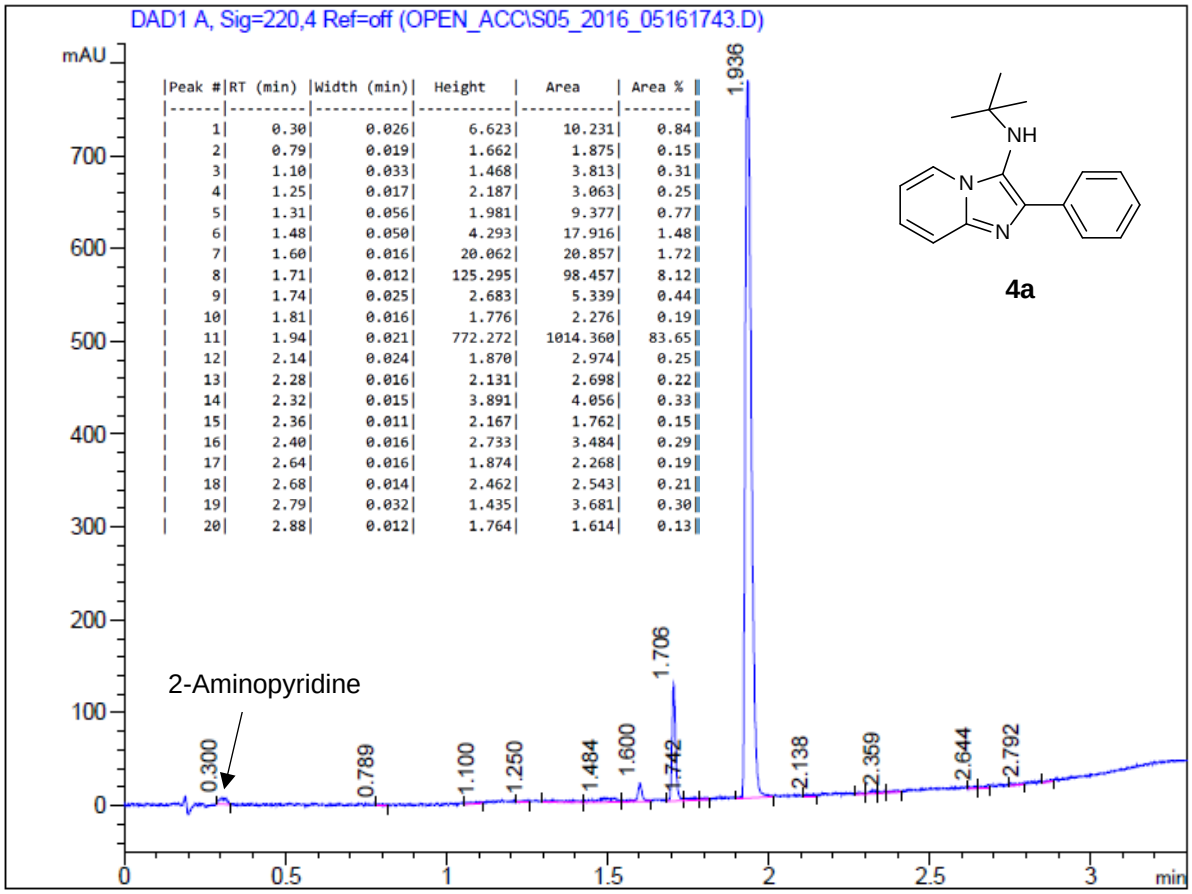
7.3
7.8
9.0
9.0
7.8
7.9
7.8
7.8
DMSO-d6
DMSO-d6
DMSO-d6
TMS
4.7
4.6
4.6
4.6
4.6
4.6
4.6
4.6
4.6
1.00
1.94
0.97
2.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)


NH2
Br
N
N

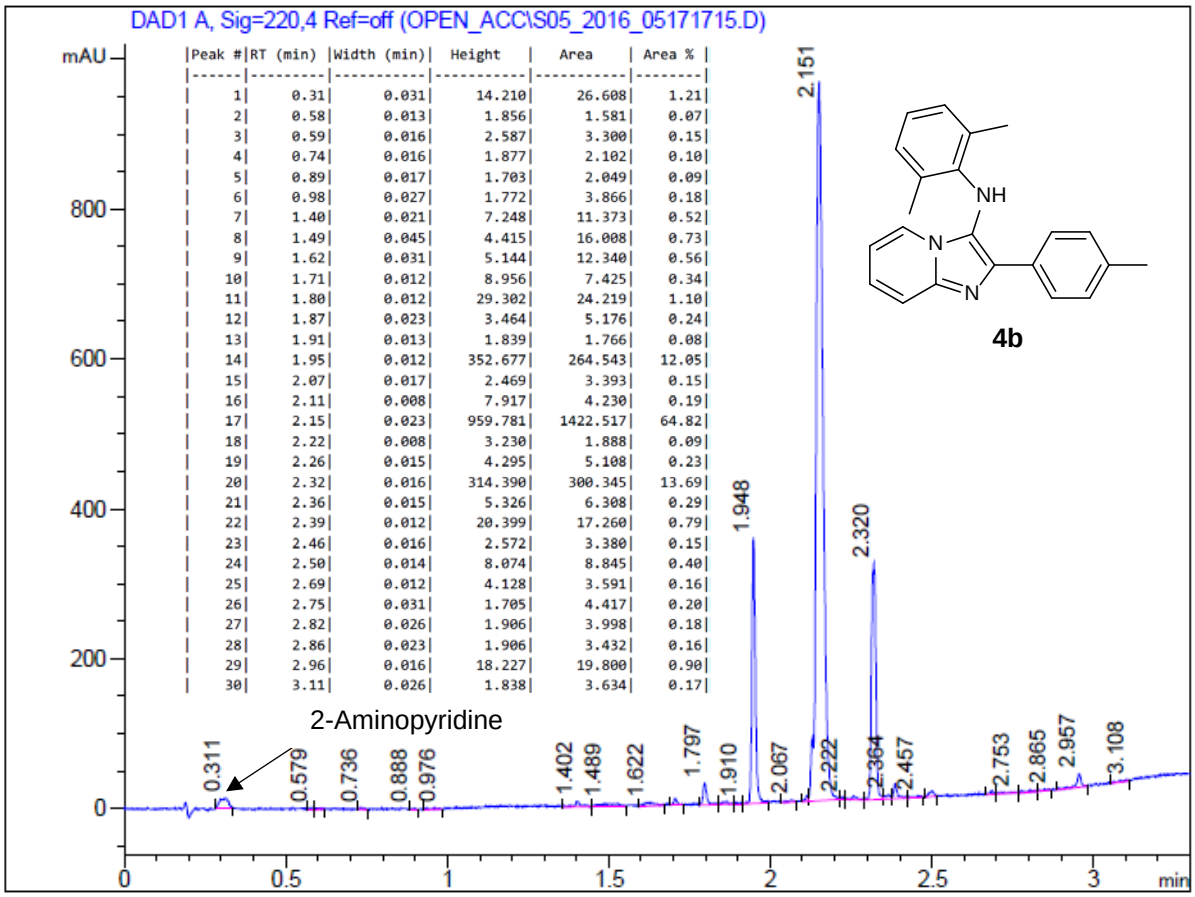
4ab


DMSO-d6
132.9
133.5
134.0
124.9
113.7
109.8
103.3
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)

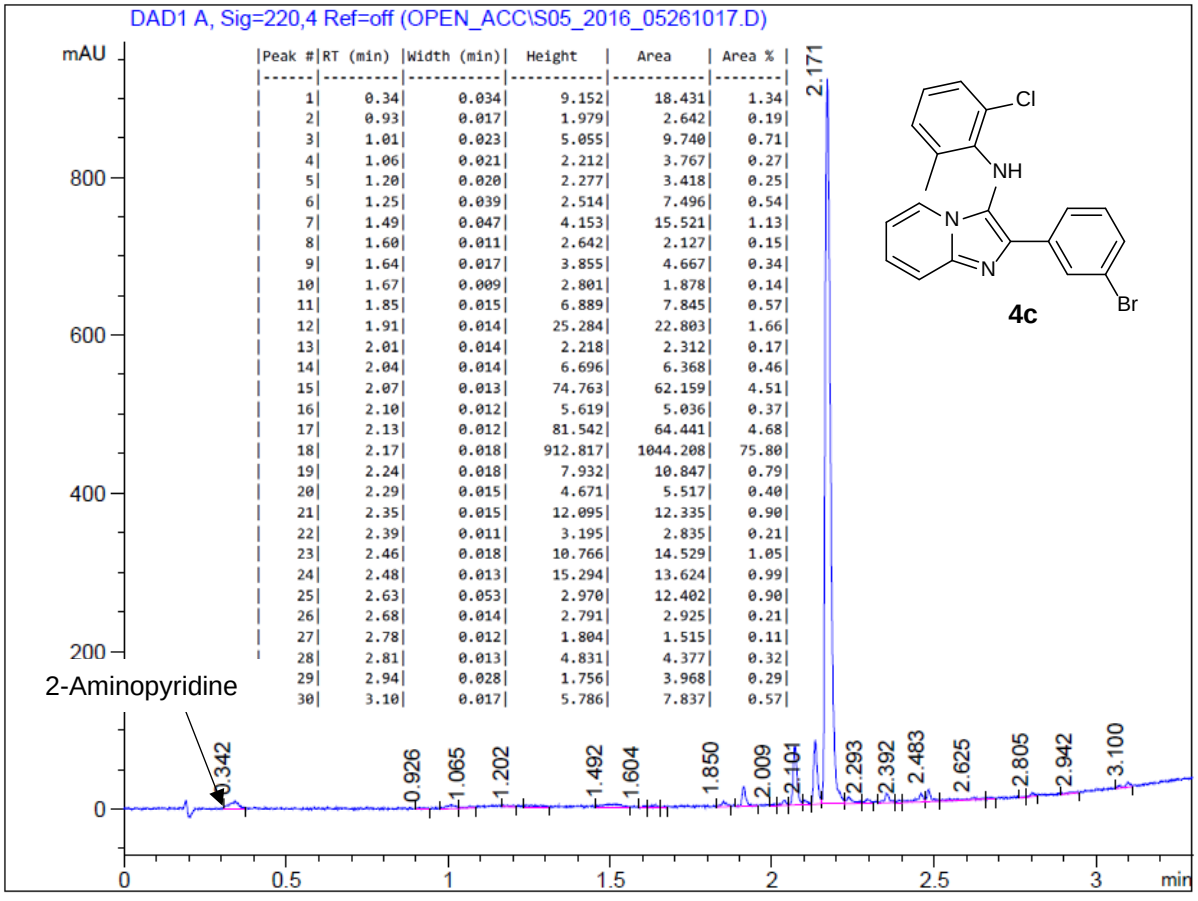
7. HPLC data for reaction profiles



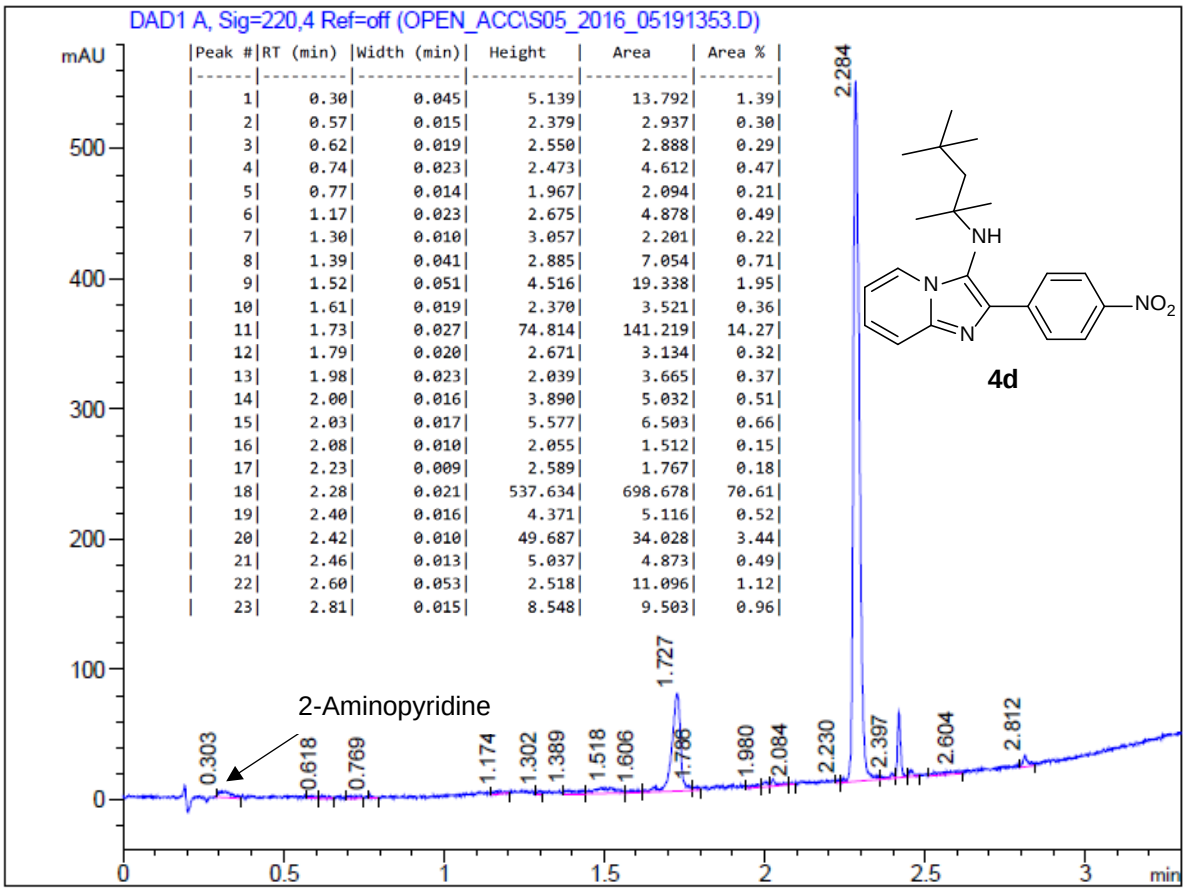
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.30	0.026	6.623	10.231	0.84
2	0.79	0.019	1.662	1.875	0.15
3	1.10	0.033	1.468	3.813	0.31
4	1.25	0.017	2.187	3.063	0.25
5	1.31	0.056	1.981	9.377	0.77
6	1.48	0.050	4.293	17.916	1.48
7	1.60	0.016	20.062	20.857	1.72
8	1.71	0.012	125.295	98.457	8.12
9	1.74	0.025	2.683	5.339	0.44
10	1.81	0.016	1.776	2.276	0.19
11	1.94	0.021	772.272	1014.360	83.65
12	2.14	0.024	1.870	2.974	0.25
13	2.28	0.016	2.131	2.698	0.22
14	2.32	0.015	3.891	4.056	0.33
15	2.36	0.011	2.167	1.762	0.15
16	2.40	0.016	2.733	3.484	0.29
17	2.64	0.016	1.874	2.268	0.19
18	2.68	0.014	2.462	2.543	0.21
19	2.79	0.032	1.435	3.681	0.30
20	2.88	0.012	1.764	1.614	0.13



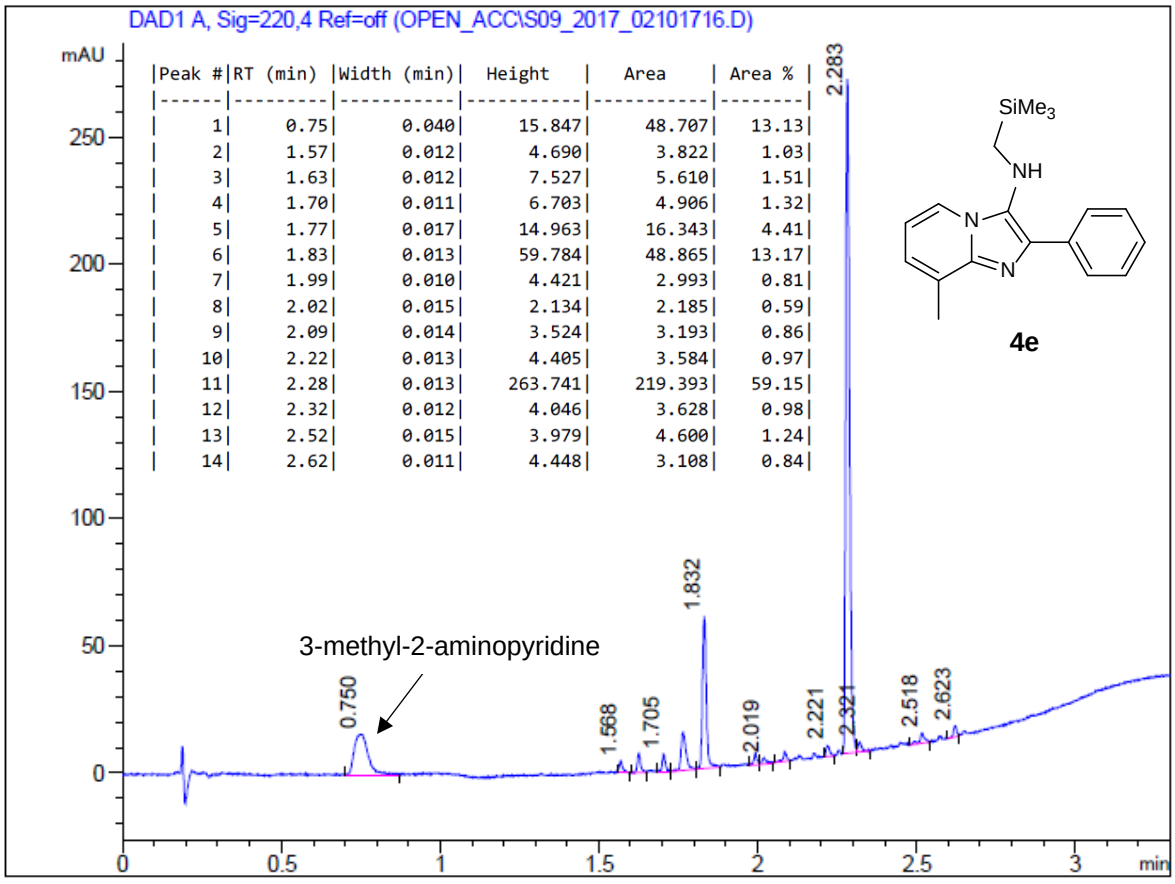
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.31	0.031	14.210	26.608	1.21
2	0.58	0.013	1.856	1.581	0.07
3	0.59	0.016	2.587	3.300	0.15
4	0.74	0.016	1.877	2.102	0.10
5	0.89	0.017	1.703	2.049	0.09
6	0.98	0.027	1.772	3.866	0.18
7	1.40	0.021	7.248	11.373	0.52
8	1.49	0.045	4.415	16.008	0.73
9	1.62	0.031	5.144	12.340	0.56
10	1.71	0.012	8.956	7.425	0.34
11	1.80	0.012	29.302	24.219	1.10
12	1.87	0.023	3.464	5.176	0.24
13	1.91	0.013	1.839	1.766	0.08
14	1.95	0.012	352.677	264.543	12.05
15	2.07	0.017	2.469	3.393	0.15
16	2.11	0.008	7.917	4.230	0.19
17	2.15	0.023	959.781	1422.517	64.82
18	2.22	0.008	3.230	1.888	0.09
19	2.26	0.015	4.295	5.108	0.23
20	2.32	0.016	314.390	300.345	13.69
21	2.36	0.015	5.326	6.308	0.29
22	2.39	0.012	20.399	17.260	0.79
23	2.46	0.016	2.572	3.380	0.15
24	2.50	0.014	8.074	8.845	0.40
25	2.69	0.012	4.128	3.591	0.16
26	2.75	0.031	1.705	4.417	0.20
27	2.82	0.026	1.906	3.998	0.18
28	2.86	0.023	1.906	3.432	0.16
29	2.96	0.016	18.227	19.800	0.90
30	3.11	0.026	1.838	3.634	0.17



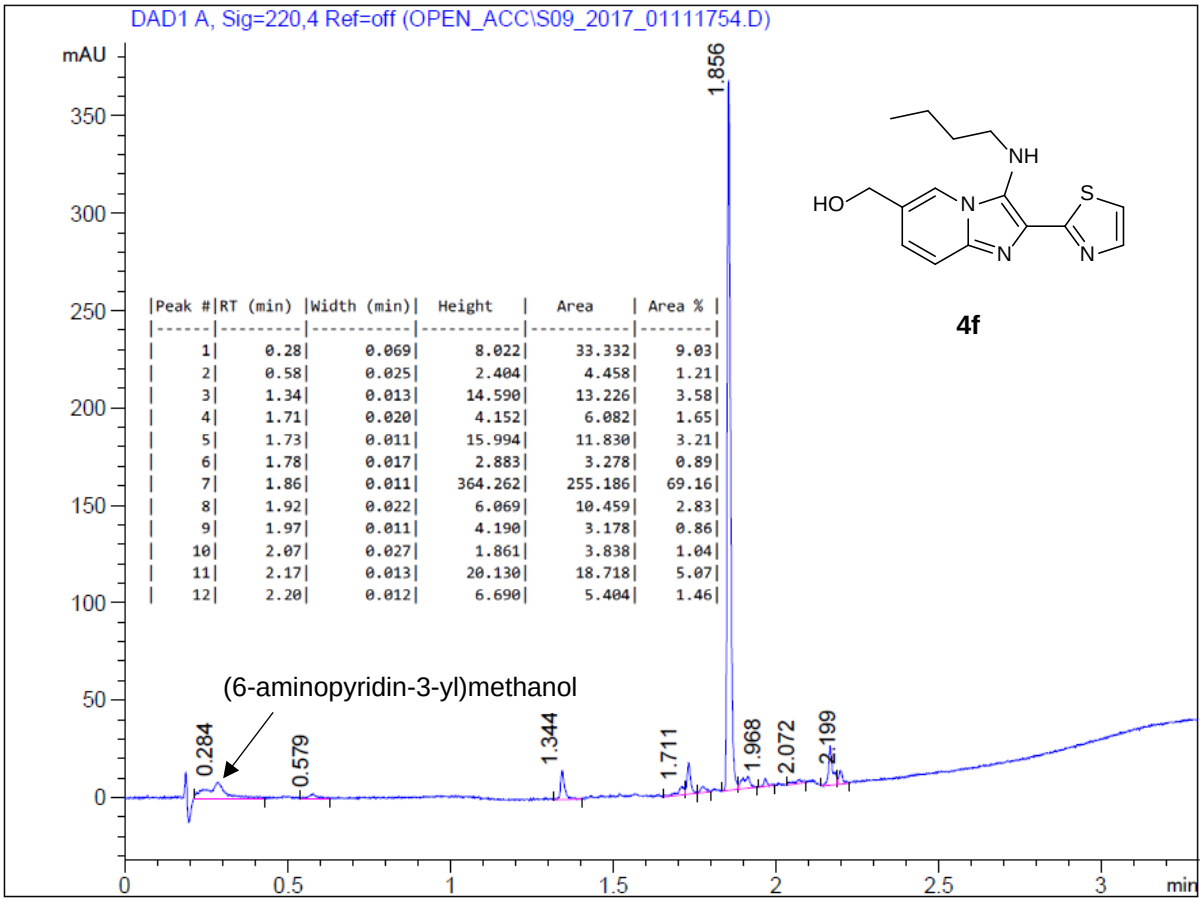
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.34	0.034	9.152	18.431	1.34
2	0.93	0.017	1.979	2.642	0.19
3	1.01	0.023	5.055	9.740	0.71
4	1.06	0.021	2.212	3.767	0.27
5	1.20	0.020	2.277	3.418	0.25
6	1.25	0.039	2.514	7.496	0.54
7	1.49	0.047	4.153	15.521	1.13
8	1.60	0.011	2.642	2.127	0.15
9	1.64	0.017	3.855	4.667	0.34
10	1.67	0.009	2.801	1.878	0.14
11	1.85	0.015	6.889	7.845	0.57
12	1.91	0.014	25.284	22.803	1.66
13	2.01	0.014	2.218	2.312	0.17
14	2.04	0.014	6.696	6.368	0.46
15	2.07	0.013	74.763	62.159	4.51
16	2.10	0.012	5.619	5.036	0.37
17	2.13	0.012	81.542	64.441	4.68
18	2.17	0.018	912.817	1044.208	75.80
19	2.24	0.018	7.932	10.847	0.79
20	2.29	0.015	4.671	5.517	0.40
21	2.35	0.015	12.095	12.335	0.90
22	2.39	0.011	3.195	2.835	0.21
23	2.46	0.018	10.766	14.529	1.05
24	2.48	0.013	15.294	13.624	0.99
25	2.63	0.053	2.970	12.402	0.90
26	2.68	0.014	2.791	2.925	0.21
27	2.78	0.012	1.804	1.515	0.11
28	2.81	0.013	4.831	4.377	0.32
29	2.94	0.028	1.756	3.968	0.29
30	3.10	0.017	5.786	7.837	0.57



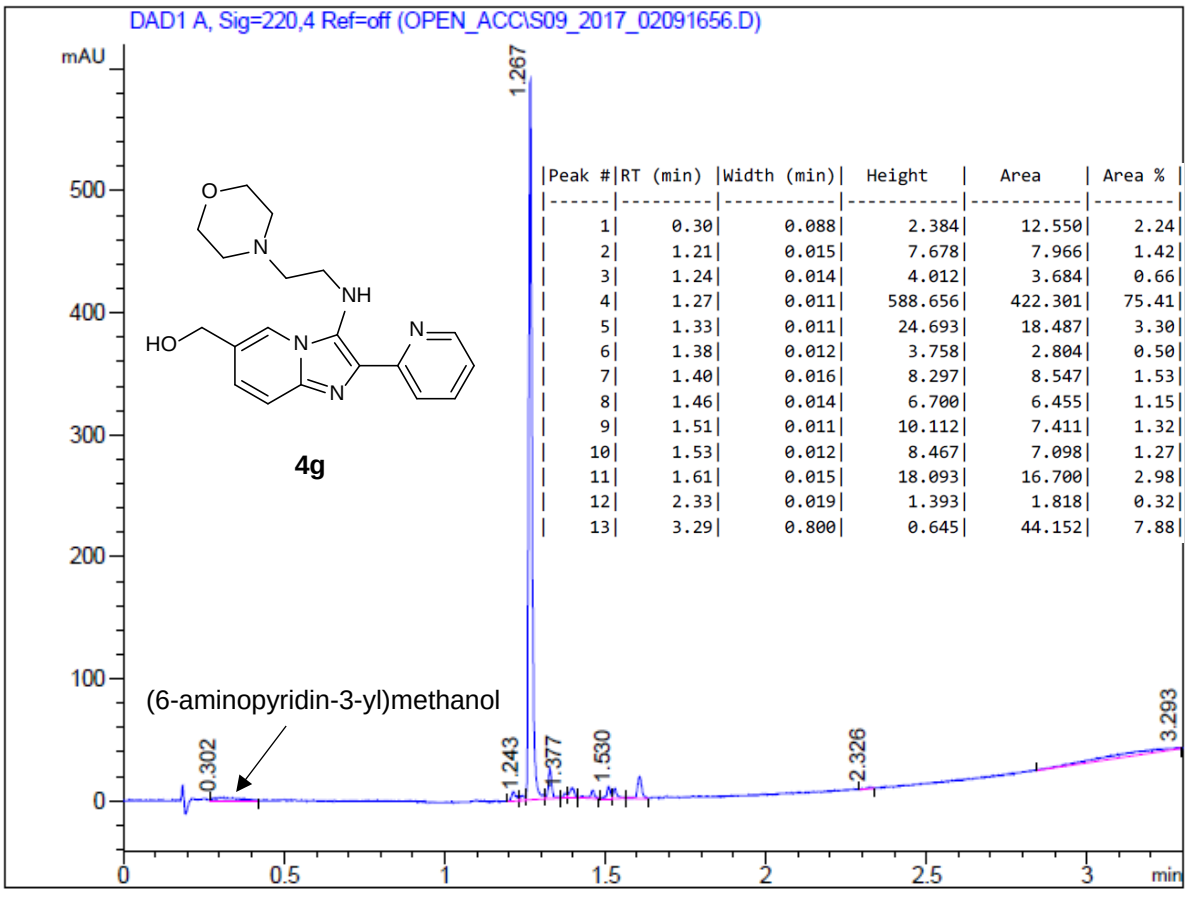
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.30	0.045	5.139	13.792	1.39
2	0.57	0.015	2.379	2.937	0.30
3	0.62	0.019	2.550	2.888	0.29
4	0.74	0.023	2.473	4.612	0.47
5	0.77	0.014	1.967	2.094	0.21
6	1.17	0.023	2.675	4.878	0.49
7	1.30	0.010	3.057	2.201	0.22
8	1.39	0.041	2.885	7.054	0.71
9	1.52	0.051	4.516	19.338	1.95
10	1.61	0.019	2.370	3.521	0.36
11	1.73	0.027	74.814	141.219	14.27
12	1.79	0.020	2.671	3.134	0.32
13	1.98	0.023	2.039	3.665	0.37
14	2.00	0.016	3.890	5.032	0.51
15	2.03	0.017	5.577	6.503	0.66
16	2.08	0.010	2.055	1.512	0.15
17	2.23	0.009	2.589	1.767	0.18
18	2.28	0.021	537.634	698.678	70.61
19	2.40	0.016	4.371	5.116	0.52
20	2.42	0.010	49.687	34.028	3.44
21	2.46	0.013	5.037	4.873	0.49
22	2.60	0.053	2.518	11.096	1.12
23	2.81	0.015	8.548	9.503	0.96



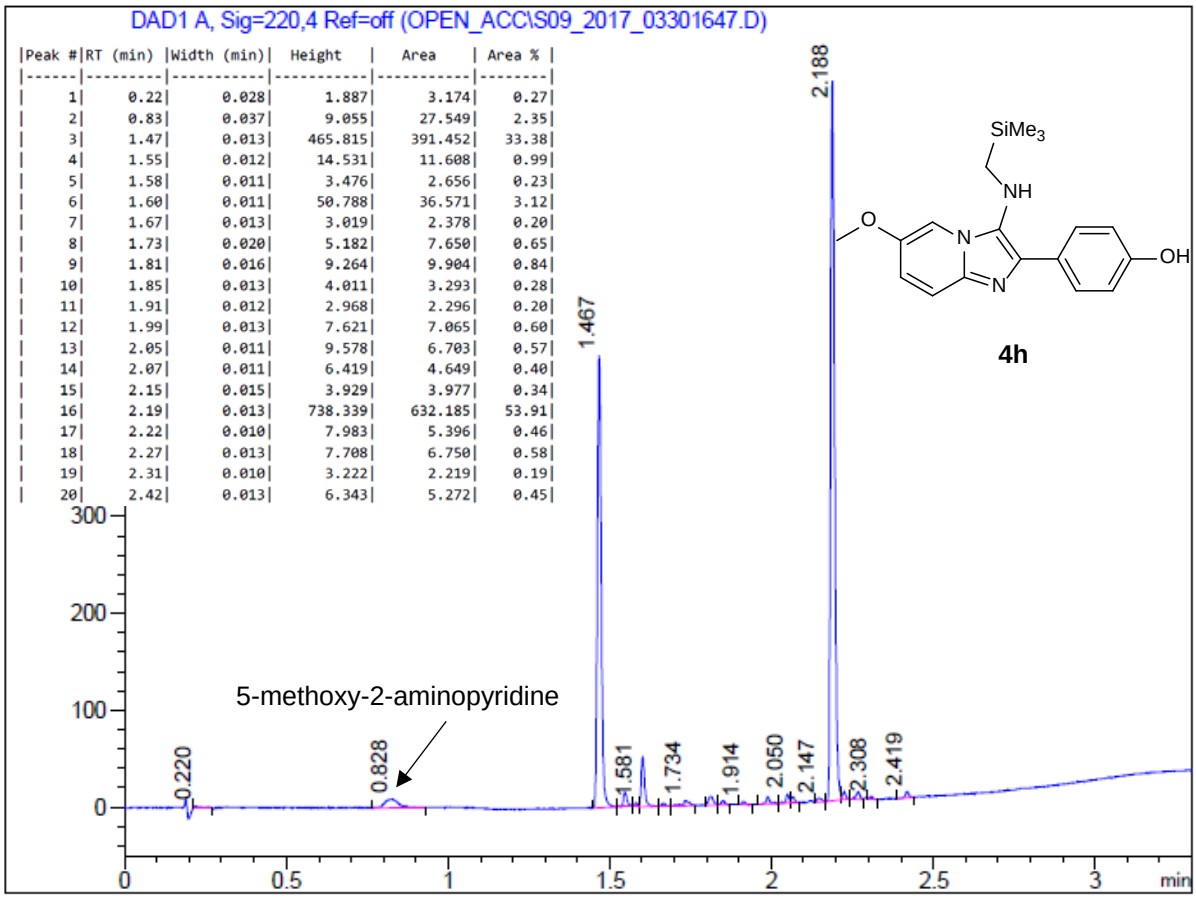
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.75	0.040	15.847	48.707	13.13
2	1.57	0.012	4.690	3.822	1.03
3	1.63	0.012	7.527	5.610	1.51
4	1.70	0.011	6.703	4.906	1.32
5	1.77	0.017	14.963	16.343	4.41
6	1.83	0.013	59.784	48.865	13.17
7	1.99	0.010	4.421	2.993	0.81
8	2.02	0.015	2.134	2.185	0.59
9	2.09	0.014	3.524	3.193	0.86
10	2.22	0.013	4.405	3.584	0.97
11	2.28	0.013	263.741	219.393	59.15
12	2.32	0.012	4.046	3.628	0.98
13	2.52	0.015	3.979	4.600	1.24
14	2.62	0.011	4.448	3.108	0.84



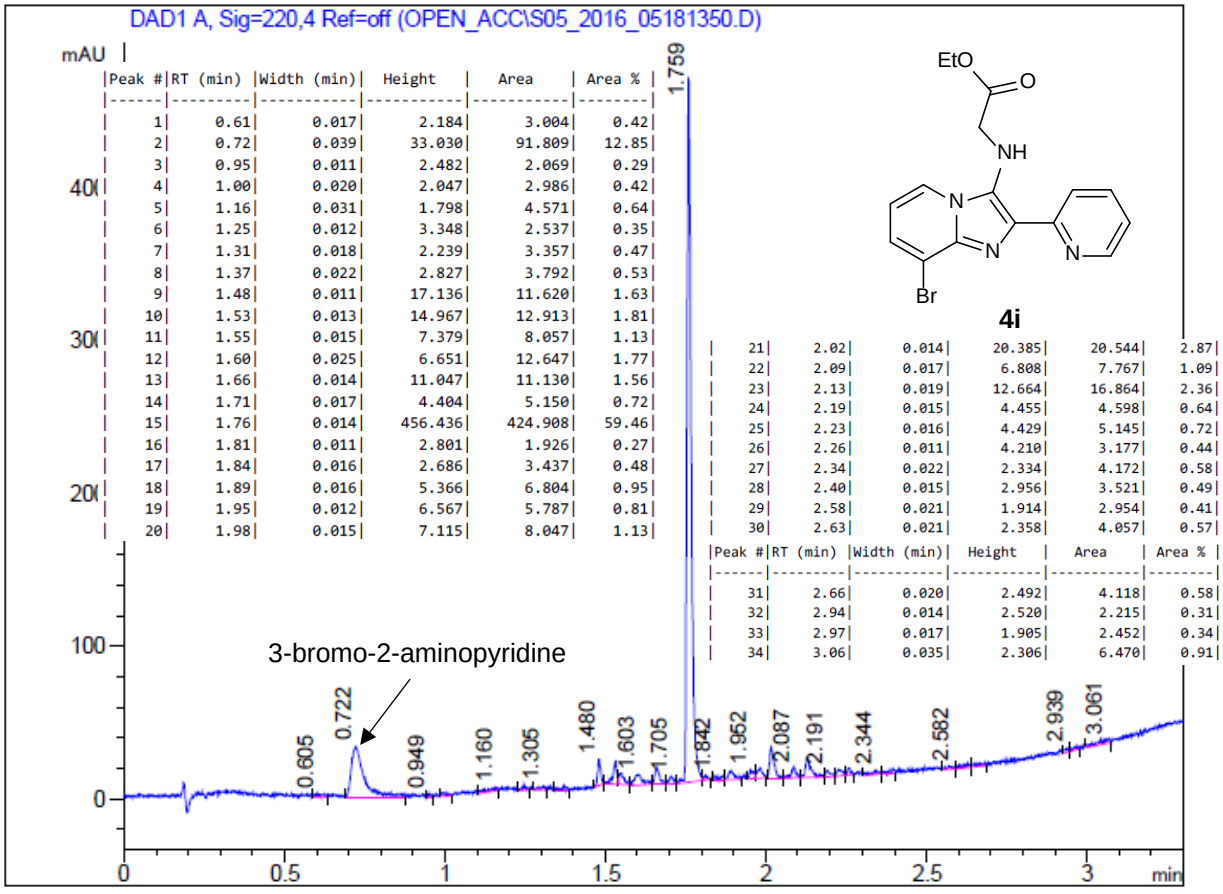
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.28	0.069	8.022	33.332	9.03
2	0.58	0.025	2.404	4.458	1.21
3	1.34	0.013	14.590	13.226	3.58
4	1.71	0.020	4.152	6.082	1.65
5	1.73	0.011	15.994	11.830	3.21
6	1.78	0.017	2.883	3.278	0.89
7	1.86	0.011	364.262	255.186	69.16
8	1.92	0.022	6.069	10.459	2.83
9	1.97	0.011	4.190	3.178	0.86
10	2.07	0.027	1.861	3.838	1.04
11	2.17	0.013	20.130	18.718	5.07
12	2.20	0.012	6.690	5.404	1.46



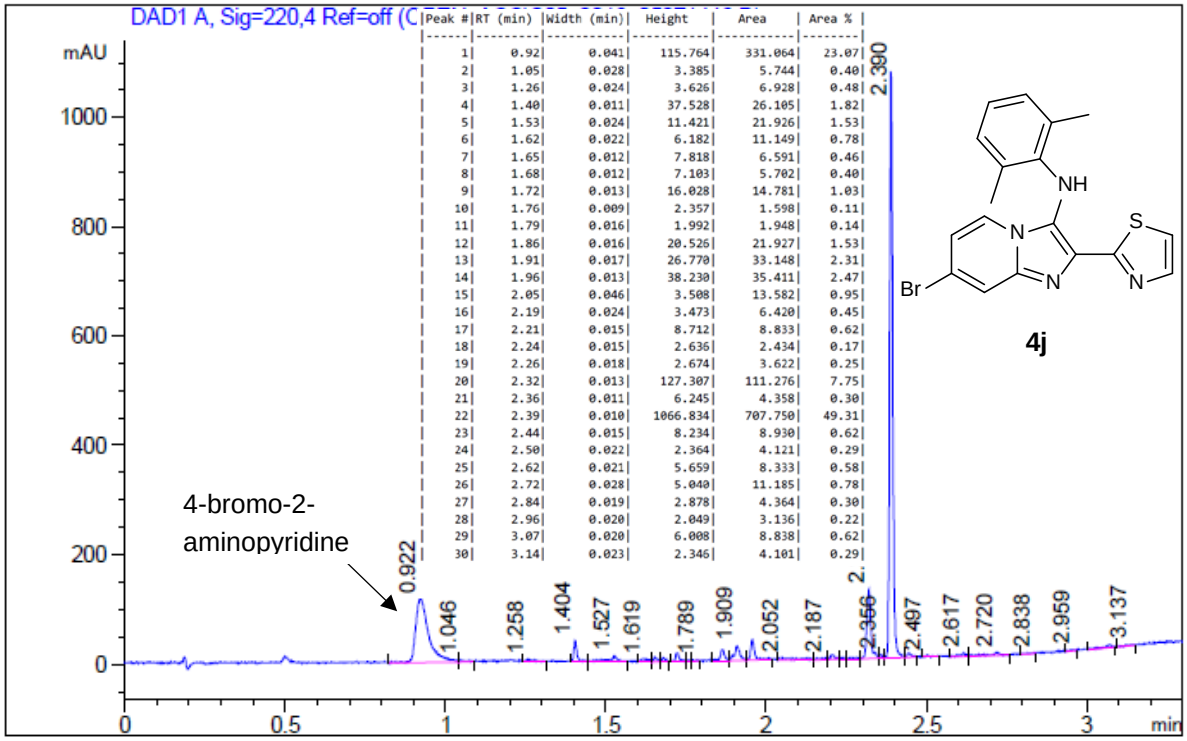
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.30	0.088	2.384	12.550	2.24
2	1.21	0.015	7.678	7.966	1.42
3	1.24	0.014	4.012	3.684	0.66
4	1.27	0.011	588.656	422.301	75.41
5	1.33	0.011	24.693	18.487	3.30
6	1.38	0.012	3.758	2.804	0.50
7	1.40	0.016	8.297	8.547	1.53
8	1.46	0.014	6.700	6.455	1.15
9	1.51	0.011	10.112	7.411	1.32
10	1.53	0.012	8.467	7.098	1.27
11	1.61	0.015	18.093	16.700	2.98
12	2.33	0.019	1.393	1.818	0.32
13	3.29	0.800	0.645	44.152	7.88



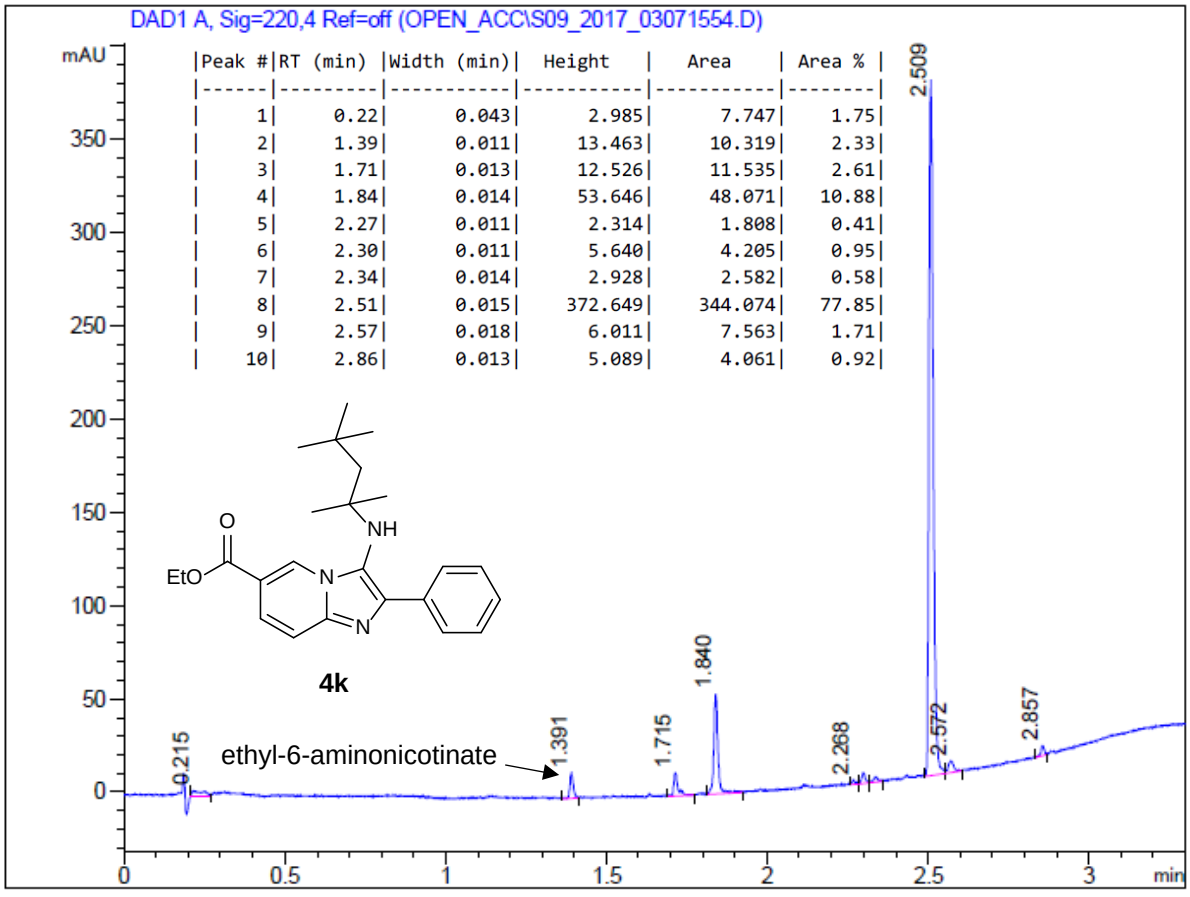
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.22	0.028	1.887	3.174	0.27
2	0.83	0.037	9.055	27.549	2.35
3	1.47	0.013	465.815	391.452	33.38
4	1.55	0.012	14.531	11.608	0.99
5	1.58	0.011	3.476	2.656	0.23
6	1.60	0.011	50.788	36.571	3.12
7	1.67	0.013	3.019	2.378	0.20
8	1.73	0.020	5.182	7.650	0.65
9	1.81	0.016	9.264	9.904	0.84
10	1.85	0.013	4.011	3.293	0.28
11	1.91	0.012	2.968	2.296	0.20
12	1.99	0.013	7.621	7.065	0.60
13	2.05	0.011	9.578	6.703	0.57
14	2.07	0.011	6.419	4.649	0.40
15	2.15	0.015	3.929	3.977	0.34
16	2.19	0.013	738.339	632.185	53.91
17	2.22	0.010	7.983	5.396	0.46
18	2.27	0.013	7.708	6.750	0.58
19	2.31	0.010	3.222	2.219	0.19
20	2.42	0.013	6.343	5.272	0.45



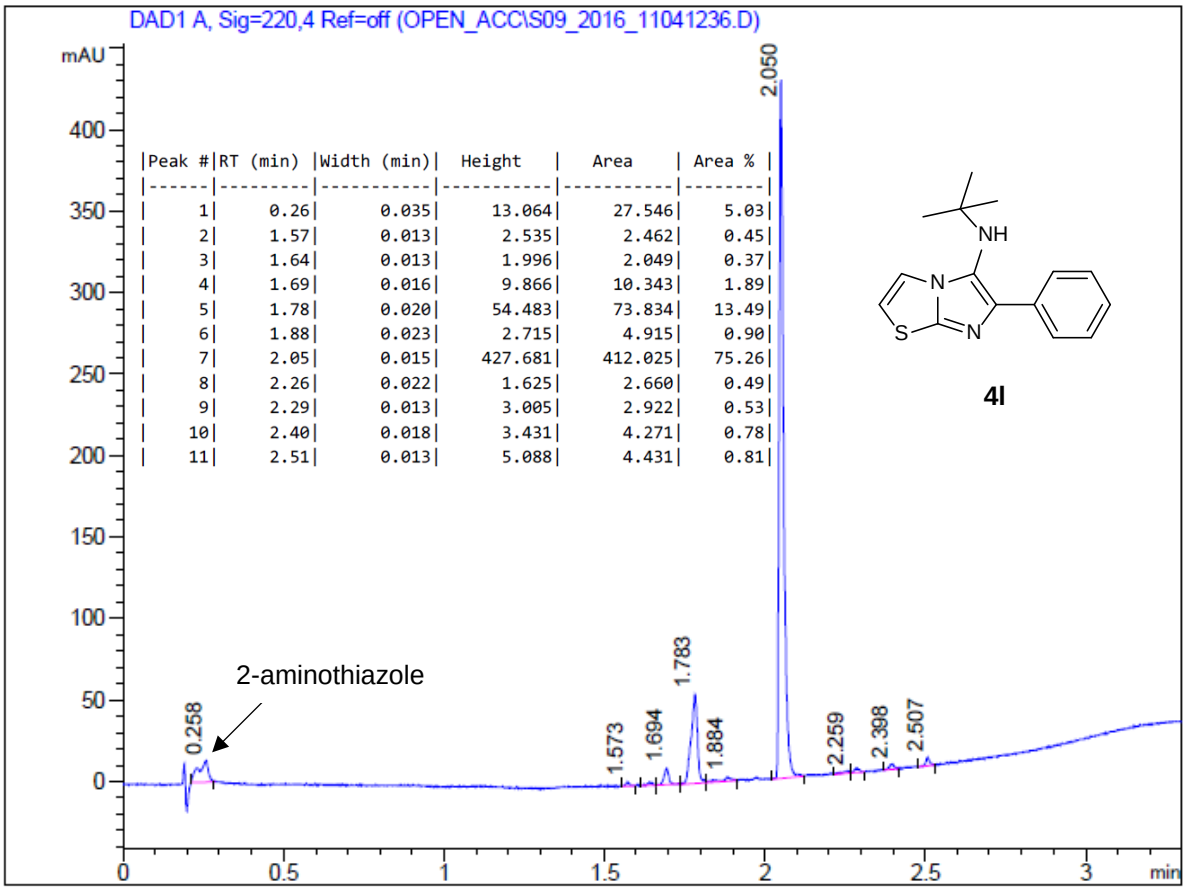
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.61	0.017	2.184	3.004	0.42
2	0.72	0.039	33.030	91.809	12.85
3	0.95	0.011	2.482	2.069	0.29
4	1.00	0.020	2.047	2.986	0.42
5	1.16	0.031	1.798	4.571	0.64
6	1.25	0.012	3.348	2.537	0.35
7	1.31	0.018	2.239	3.357	0.47
8	1.37	0.022	2.827	3.792	0.53
9	1.48	0.011	17.136	11.620	1.63
10	1.53	0.013	14.967	12.913	1.81
11	1.55	0.015	7.379	8.057	1.13
12	1.60	0.025	6.651	12.647	1.77
13	1.66	0.014	11.047	11.130	1.56
14	1.71	0.017	4.404	5.150	0.72
15	1.76	0.014	456.436	424.908	59.46
16	1.81	0.011	2.801	1.926	0.27
17	1.84	0.016	2.686	3.437	0.48
18	1.89	0.016	5.366	6.804	0.95
19	1.95	0.012	6.567	5.787	0.81
20	1.98	0.015	7.115	8.047	1.13
21	2.02	0.014	20.385	20.544	2.87
22	2.09	0.017	6.808	7.767	1.09
23	2.13	0.019	12.664	16.864	2.36
24	2.19	0.015	4.455	4.598	0.64
25	2.23	0.016	4.429	5.145	0.72
26	2.26	0.011	4.210	3.177	0.44
27	2.34	0.022	2.334	4.172	0.58
28	2.40	0.015	2.956	3.521	0.49
29	2.58	0.021	1.914	2.954	0.41
30	2.63	0.021	2.358	4.057	0.57
31	2.66	0.020	2.492	4.118	0.58
32	2.94	0.014	2.520	2.215	0.31
33	2.97	0.017	1.905	2.452	0.34
34	3.06	0.035	2.306	6.470	0.91



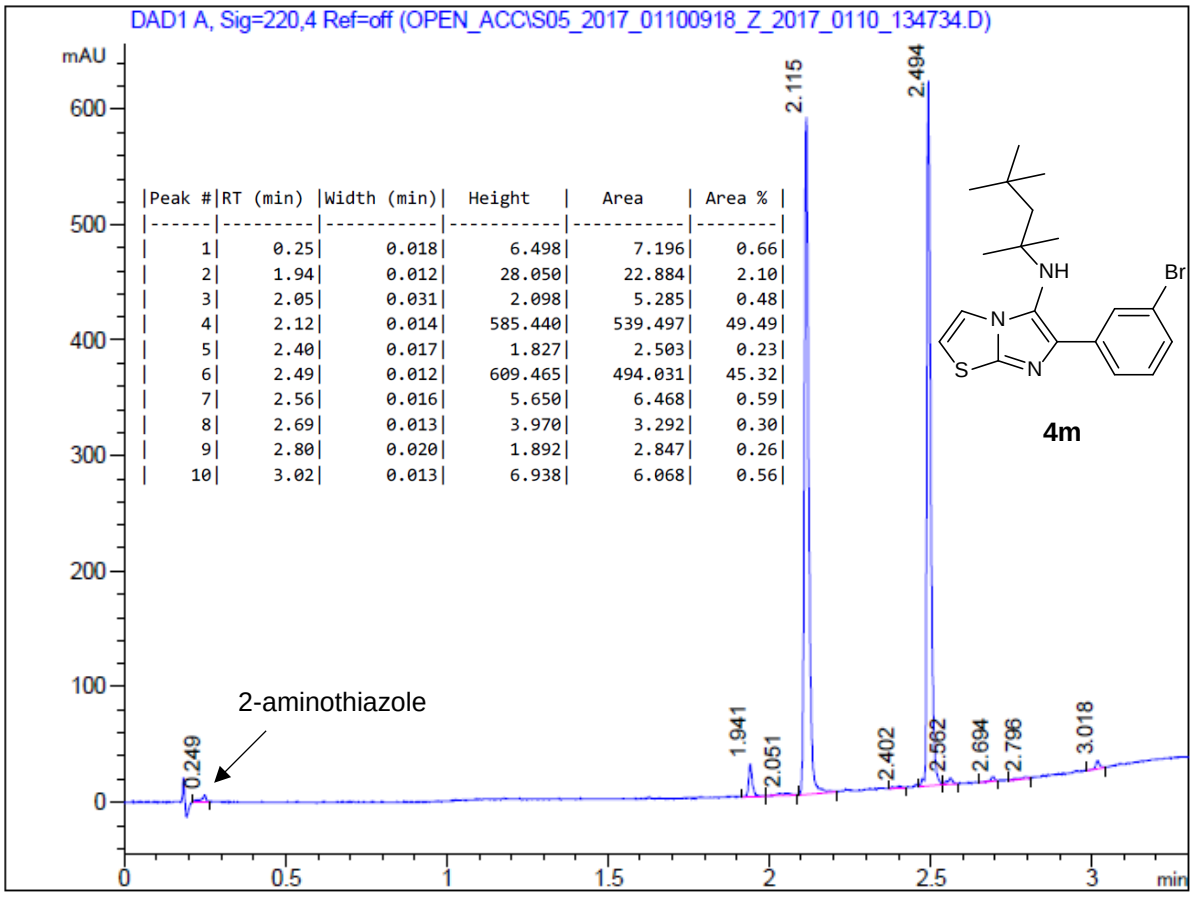
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.92	0.041	115.764	331.064	23.07
2	1.05	0.028	3.385	5.744	0.40
3	1.26	0.024	3.626	6.928	0.48
4	1.40	0.011	37.528	26.105	1.82
5	1.53	0.024	11.421	21.926	1.53
6	1.62	0.022	6.182	11.149	0.78
7	1.65	0.012	7.818	6.591	0.46
8	1.68	0.012	7.103	5.702	0.40
9	1.72	0.013	16.028	14.781	1.03
10	1.76	0.009	2.357	1.598	0.11
11	1.79	0.016	1.992	1.948	0.14
12	1.86	0.016	20.526	21.927	1.53
13	1.91	0.017	26.770	33.148	2.31
14	1.96	0.013	38.230	35.411	2.47
15	2.05	0.046	3.508	13.582	0.95
16	2.19	0.024	3.473	6.420	0.45
17	2.21	0.015	8.712	8.833	0.62
18	2.24	0.015	2.636	2.434	0.17
19	2.26	0.018	2.674	3.622	0.25
20	2.32	0.013	127.307	111.276	7.75
21	2.36	0.011	6.245	4.358	0.30
22	2.39	0.010	1066.834	707.750	49.31
23	2.44	0.015	8.234	8.930	0.62
24	2.50	0.022	2.364	4.121	0.29
25	2.62	0.021	5.659	8.333	0.58
26	2.72	0.028	5.040	11.185	0.78
27	2.84	0.019	2.878	4.364	0.30
28	2.96	0.020	2.049	3.136	0.22
29	3.07	0.020	6.008	8.838	0.62
30	3.14	0.023	2.346	4.101	0.29



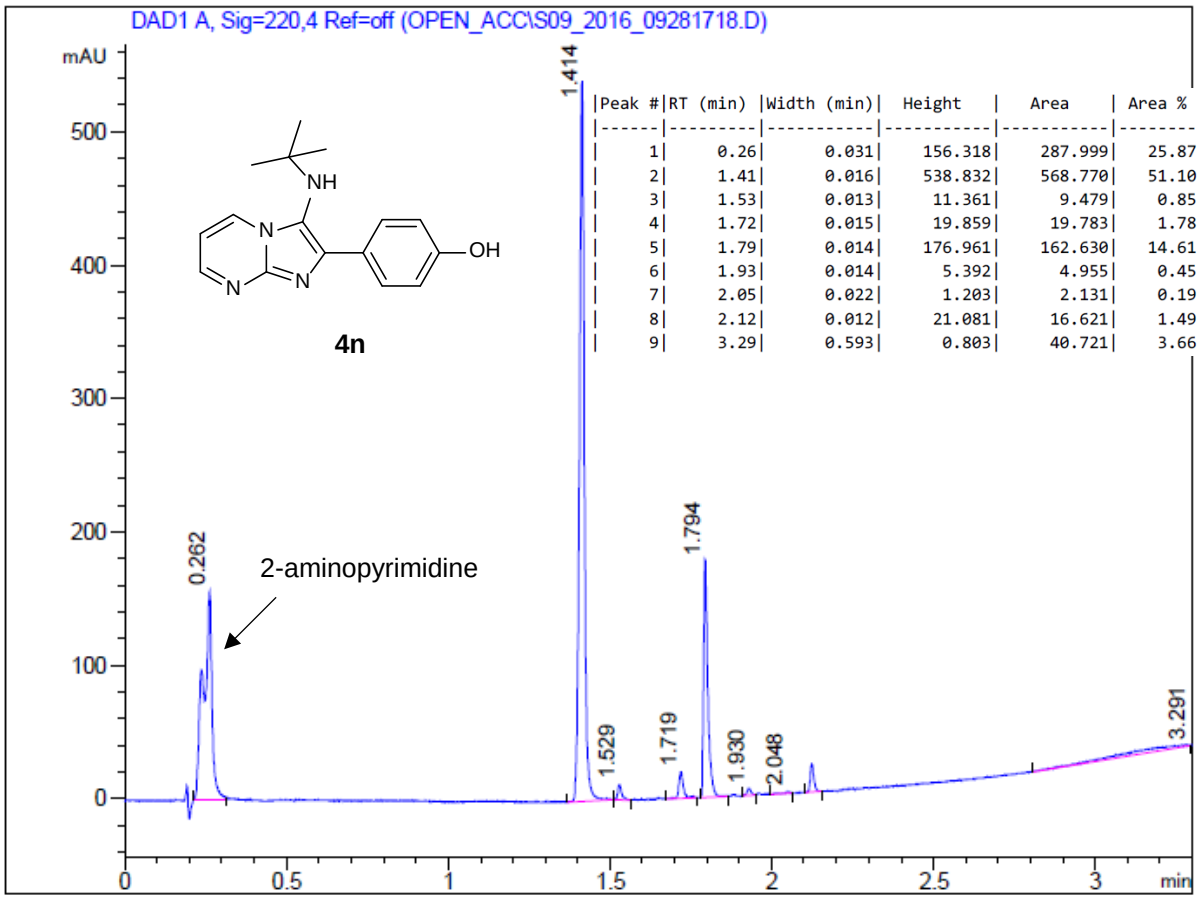
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.22	0.043	2.985	7.747	1.75
2	1.39	0.011	13.463	10.319	2.33
3	1.71	0.013	12.526	11.535	2.61
4	1.84	0.014	53.646	48.071	10.88
5	2.27	0.011	2.314	1.808	0.41
6	2.30	0.011	5.640	4.205	0.95
7	2.34	0.014	2.928	2.582	0.58
8	2.51	0.015	372.649	344.074	77.85
9	2.57	0.018	6.011	7.563	1.71
10	2.86	0.013	5.089	4.061	0.92



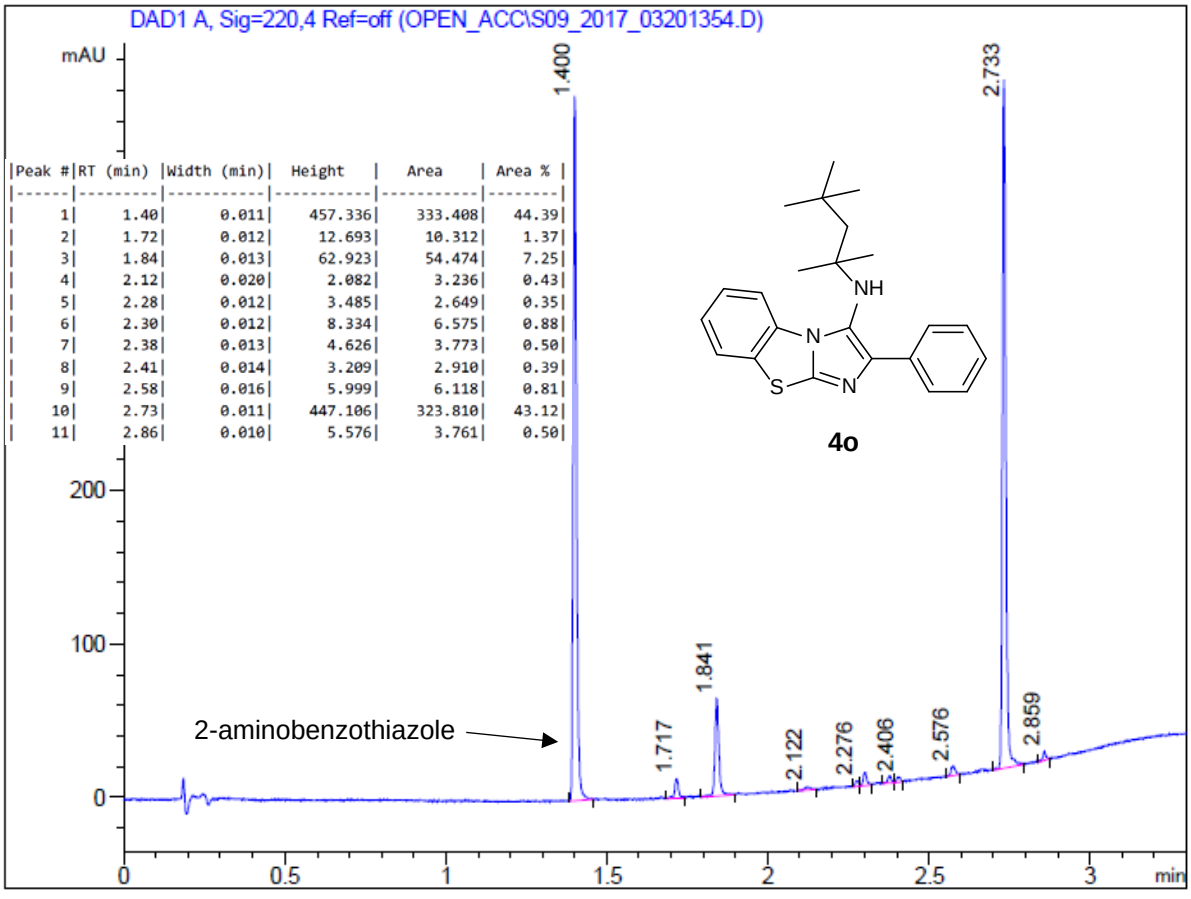
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.26	0.035	13.064	27.546	5.03
2	1.57	0.013	2.535	2.462	0.45
3	1.64	0.013	1.996	2.049	0.37
4	1.69	0.016	9.866	10.343	1.89
5	1.78	0.020	54.483	73.834	13.49
6	1.88	0.023	2.715	4.915	0.90
7	2.05	0.015	427.681	412.025	75.26
8	2.26	0.022	1.625	2.660	0.49
9	2.29	0.013	3.005	2.922	0.53
10	2.40	0.018	3.431	4.271	0.78
11	2.51	0.013	5.088	4.431	0.81



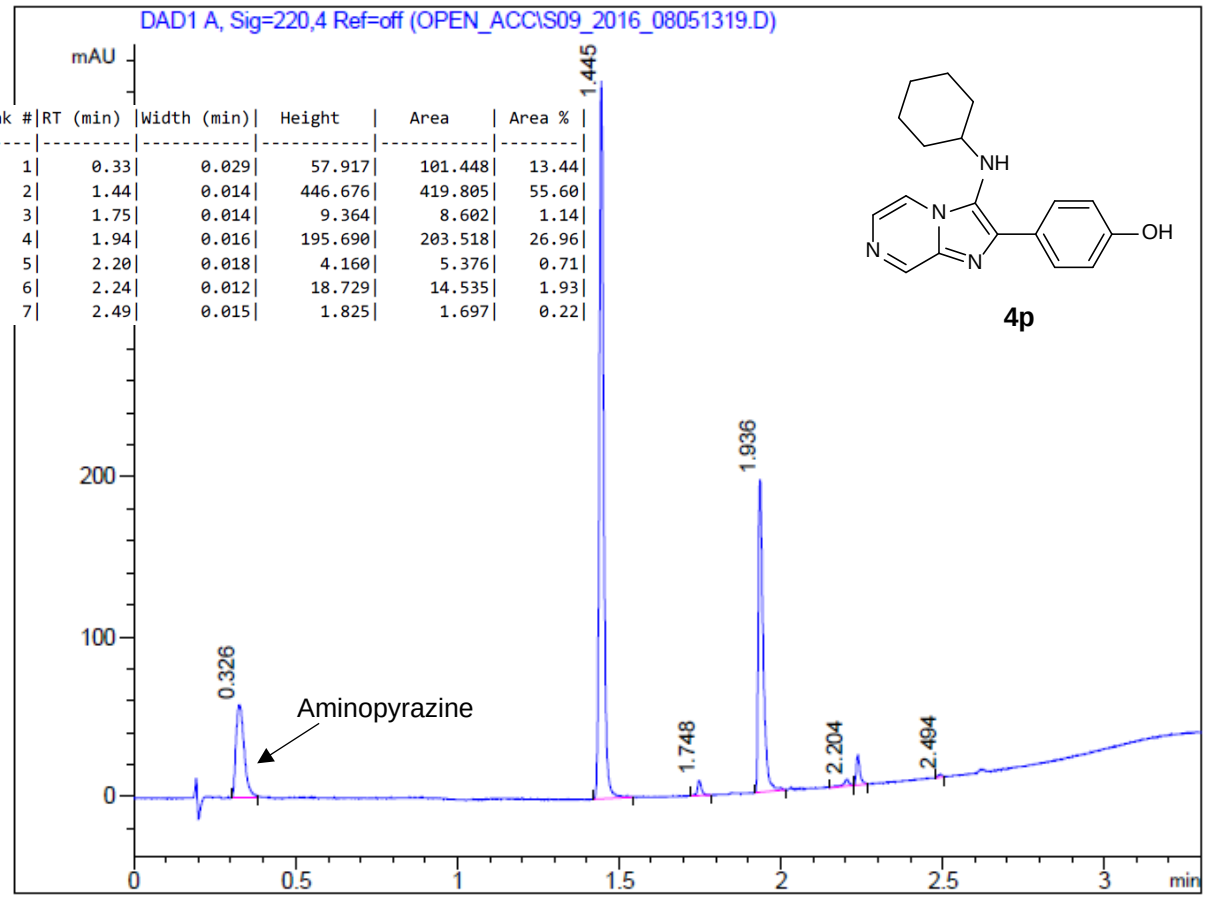
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.25	0.018	6.498	7.196	0.66
2	1.94	0.012	28.050	22.884	2.10
3	2.05	0.031	2.098	5.285	0.48
4	2.12	0.014	585.440	539.497	49.49
5	2.40	0.017	1.827	2.503	0.23
6	2.49	0.012	609.465	494.031	45.32
7	2.56	0.016	5.650	6.468	0.59
8	2.69	0.013	3.970	3.292	0.30
9	2.80	0.020	1.892	2.847	0.26
10	3.02	0.013	6.938	6.068	0.56



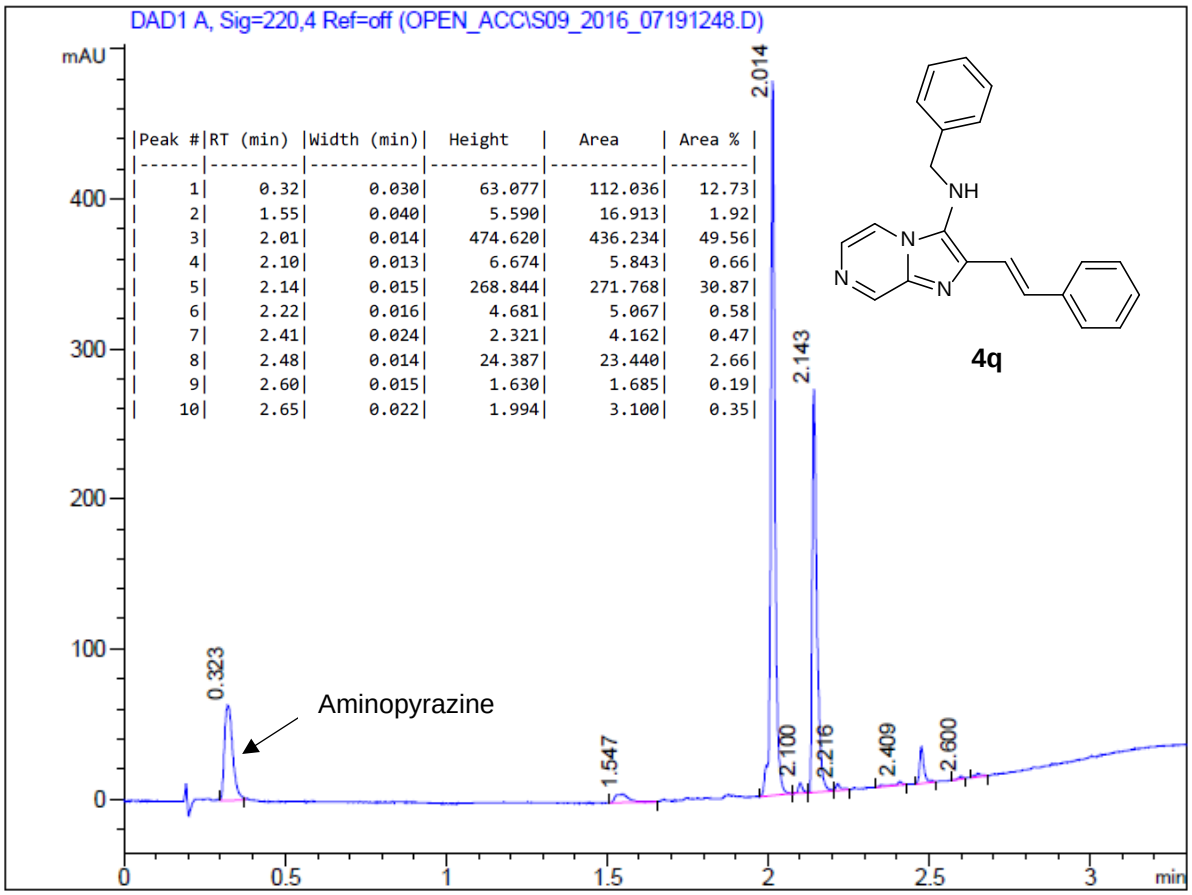
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.26	0.031	156.318	287.999	25.87
2	1.41	0.016	538.832	568.770	51.10
3	1.53	0.013	11.361	9.479	0.85
4	1.72	0.015	19.859	19.783	1.78
5	1.79	0.014	176.961	162.630	14.61
6	1.93	0.014	5.392	4.955	0.45
7	2.05	0.022	1.203	2.131	0.19
8	2.12	0.012	21.081	16.621	1.49
9	3.29	0.593	0.803	40.721	3.66



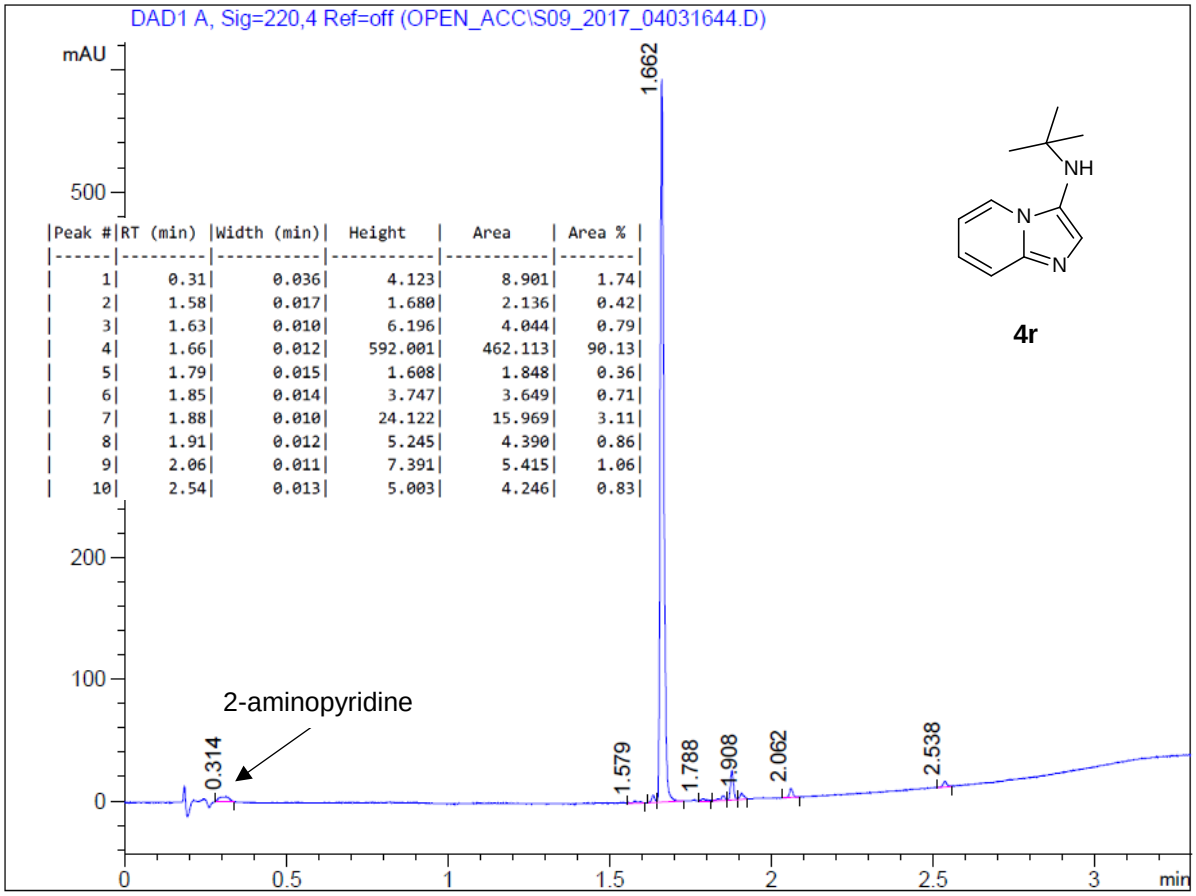
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	1.40	0.011	457.336	333.408	44.39
2	1.72	0.012	12.693	10.312	1.37
3	1.84	0.013	62.923	54.474	7.25
4	2.12	0.020	2.082	3.236	0.43
5	2.28	0.012	3.485	2.649	0.35
6	2.30	0.012	8.334	6.575	0.88
7	2.38	0.013	4.626	3.773	0.50
8	2.41	0.014	3.209	2.910	0.39
9	2.58	0.016	5.999	6.118	0.81
10	2.73	0.011	447.106	323.810	43.12
11	2.86	0.010	5.576	3.761	0.50



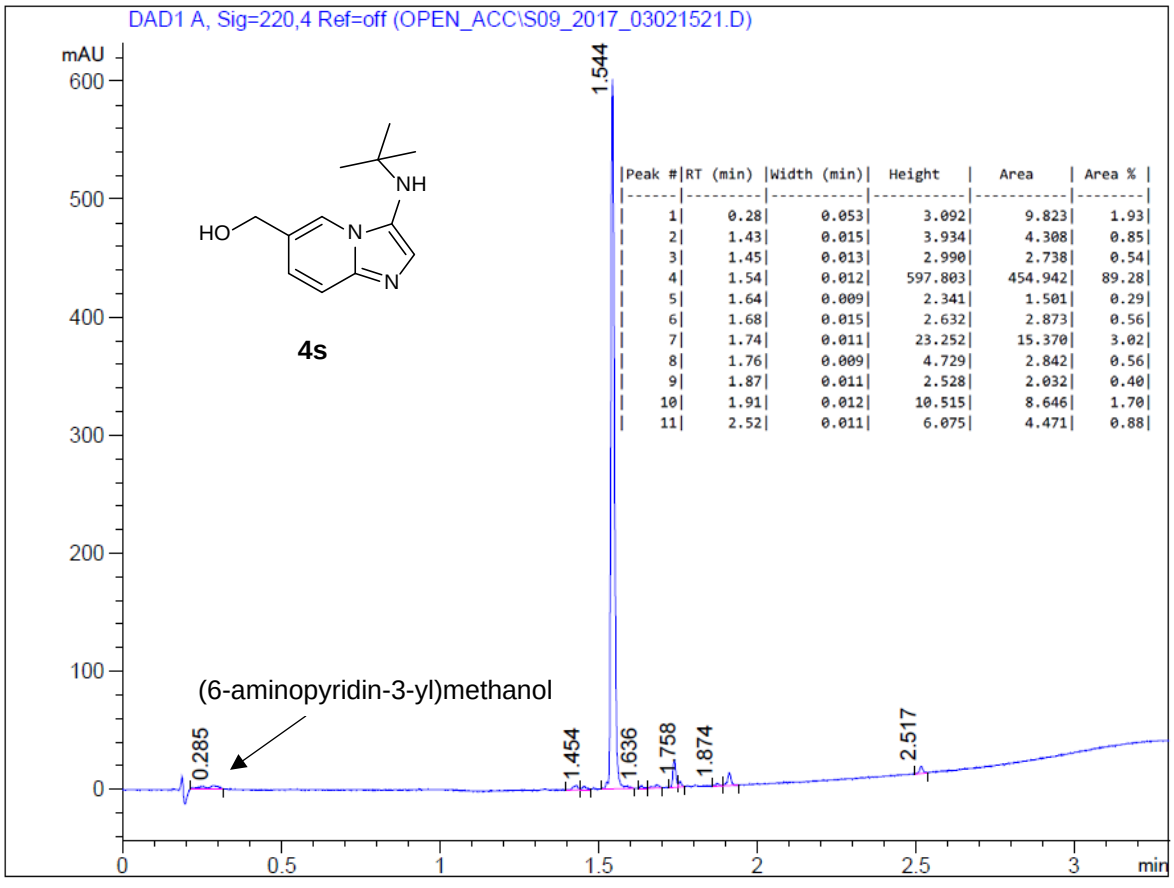
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.33	0.029	57.917	101.448	13.44
2	1.44	0.014	446.676	419.805	55.60
3	1.75	0.014	9.364	8.602	1.14
4	1.94	0.016	195.690	203.518	26.96
5	2.20	0.018	4.160	5.376	0.71
6	2.24	0.012	18.729	14.535	1.93
7	2.49	0.015	1.825	1.697	0.22



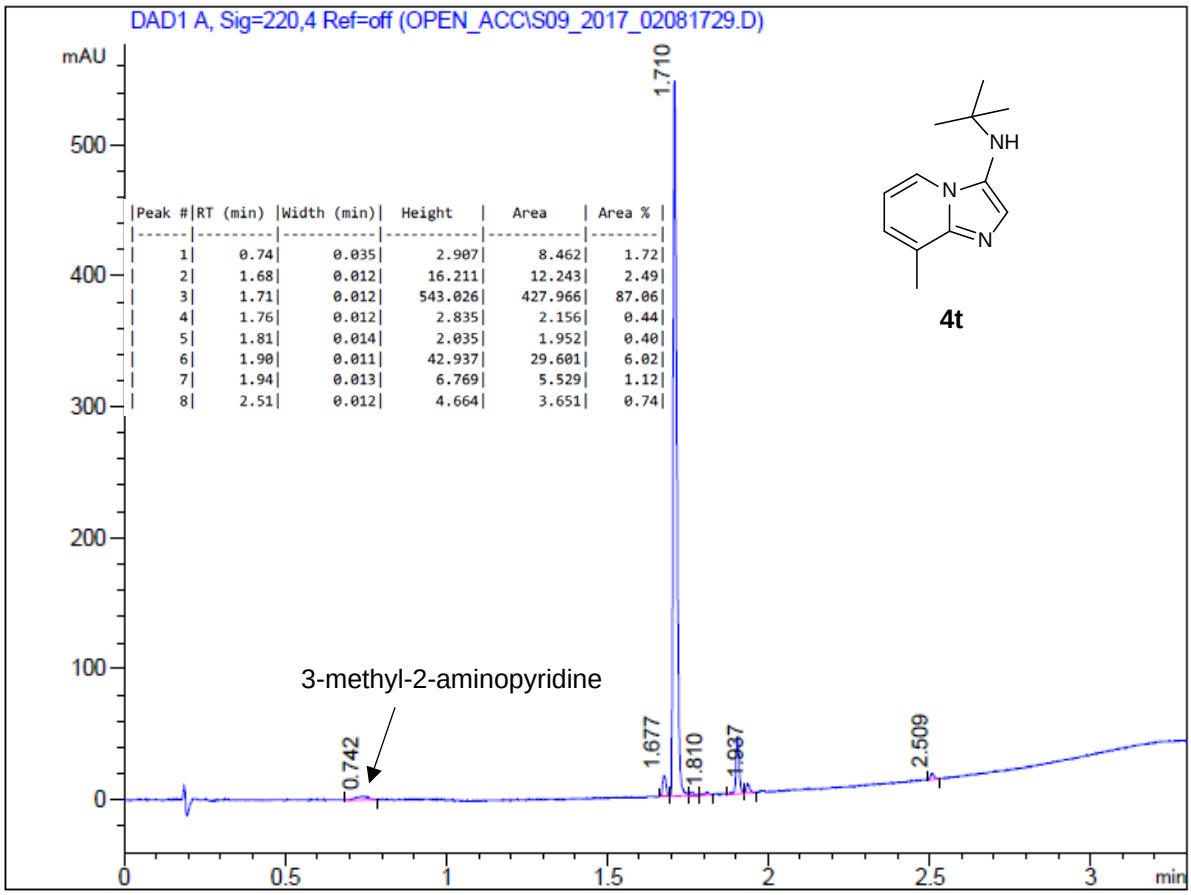
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.32	0.030	63.077	112.036	12.73
2	1.55	0.040	5.590	16.913	1.92
3	2.01	0.014	474.620	436.234	49.56
4	2.10	0.013	6.674	5.843	0.66
5	2.14	0.015	268.844	271.768	30.87
6	2.22	0.016	4.681	5.067	0.58
7	2.41	0.024	2.321	4.162	0.47
8	2.48	0.014	24.387	23.440	2.66
9	2.60	0.015	1.630	1.685	0.19
10	2.65	0.022	1.994	3.100	0.35



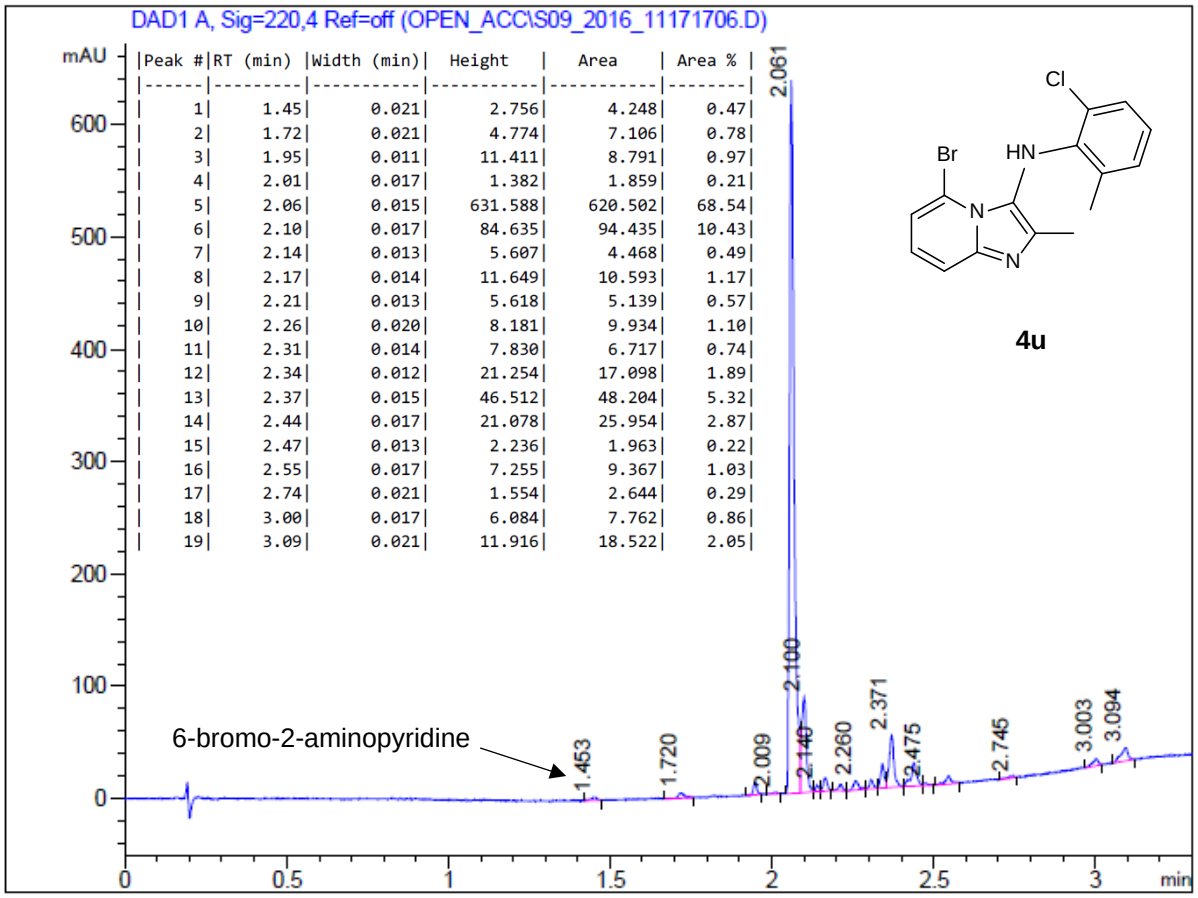
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.31	0.036	4.123	8.901	1.74
2	1.58	0.017	1.680	2.136	0.42
3	1.63	0.010	6.196	4.044	0.79
4	1.66	0.012	592.001	462.113	90.13
5	1.79	0.015	1.608	1.848	0.36
6	1.85	0.014	3.747	3.649	0.71
7	1.88	0.010	24.122	15.969	3.11
8	1.91	0.012	5.245	4.390	0.86
9	2.06	0.011	7.391	5.415	1.06
10	2.54	0.013	5.003	4.246	0.83



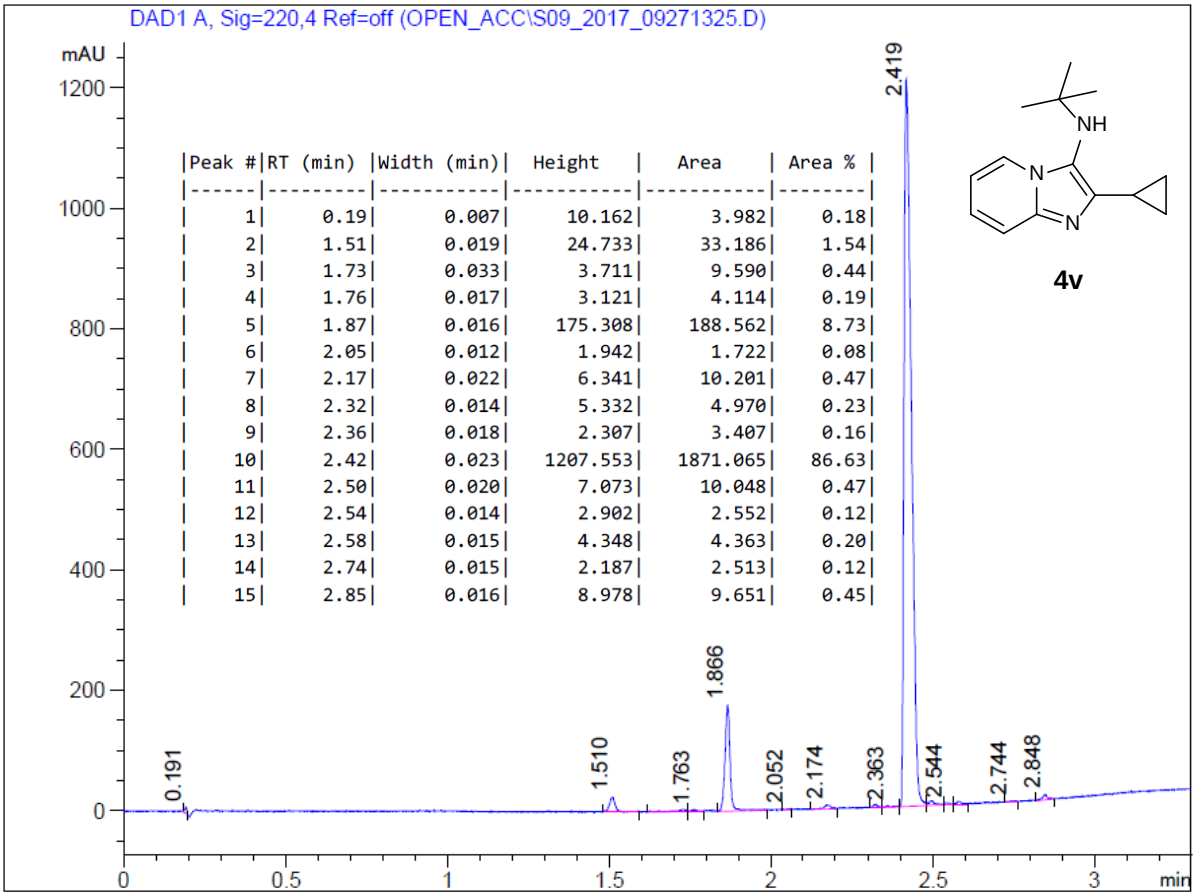
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.28	0.053	3.092	9.823	1.93
2	1.43	0.015	3.934	4.308	0.85
3	1.45	0.013	2.990	2.738	0.54
4	1.54	0.012	597.803	454.942	89.28
5	1.64	0.009	2.341	1.501	0.29
6	1.68	0.015	2.632	2.873	0.56
7	1.74	0.011	23.252	15.370	3.02
8	1.76	0.009	4.729	2.842	0.56
9	1.87	0.011	2.528	2.032	0.40
10	1.91	0.012	10.515	8.646	1.70
11	2.52	0.011	6.075	4.471	0.88



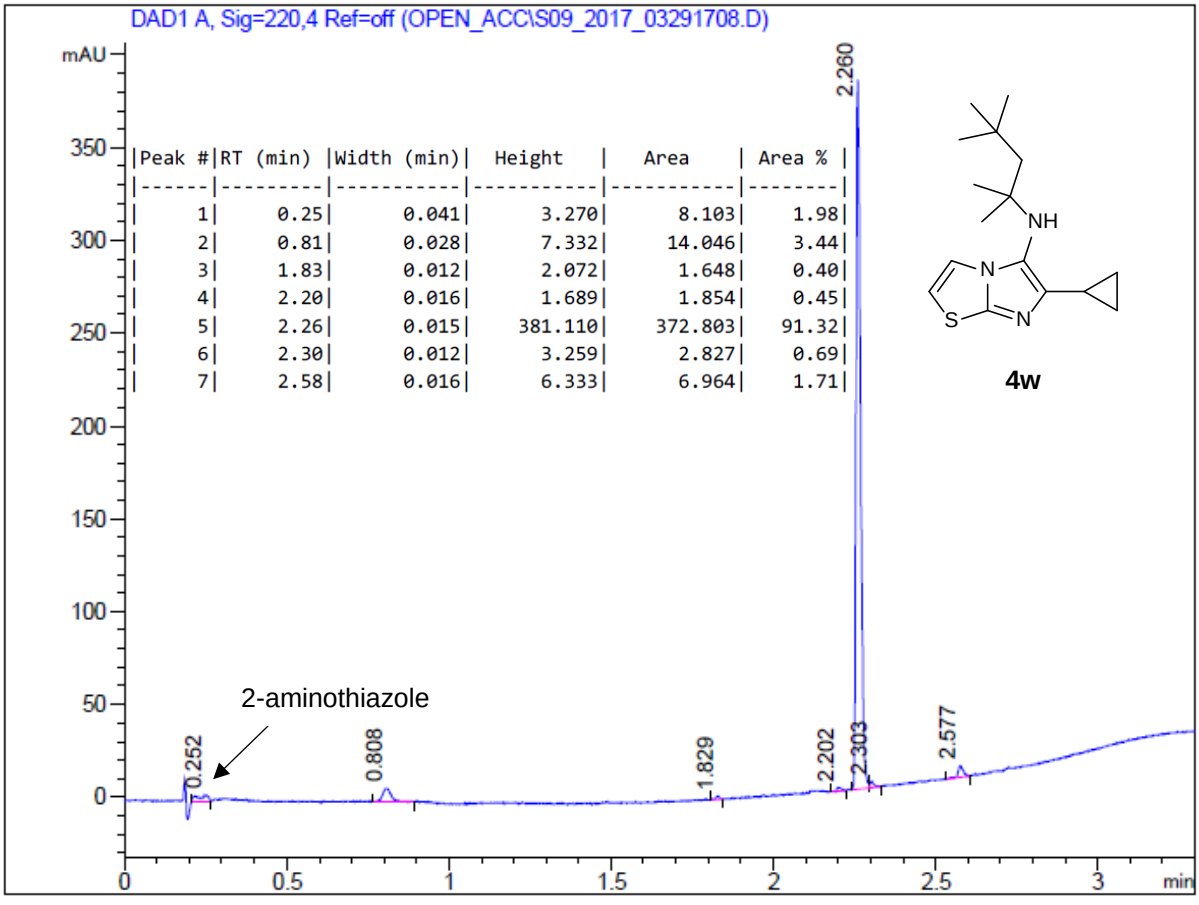
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.74	0.035	2.907	8.462	1.72
2	1.68	0.012	16.211	12.243	2.49
3	1.71	0.012	543.026	427.966	87.06
4	1.76	0.012	2.835	2.156	0.44
5	1.81	0.014	2.035	1.952	0.40
6	1.90	0.011	42.937	29.601	6.02
7	1.94	0.013	6.769	5.529	1.12
8	2.51	0.012	4.664	3.651	0.74



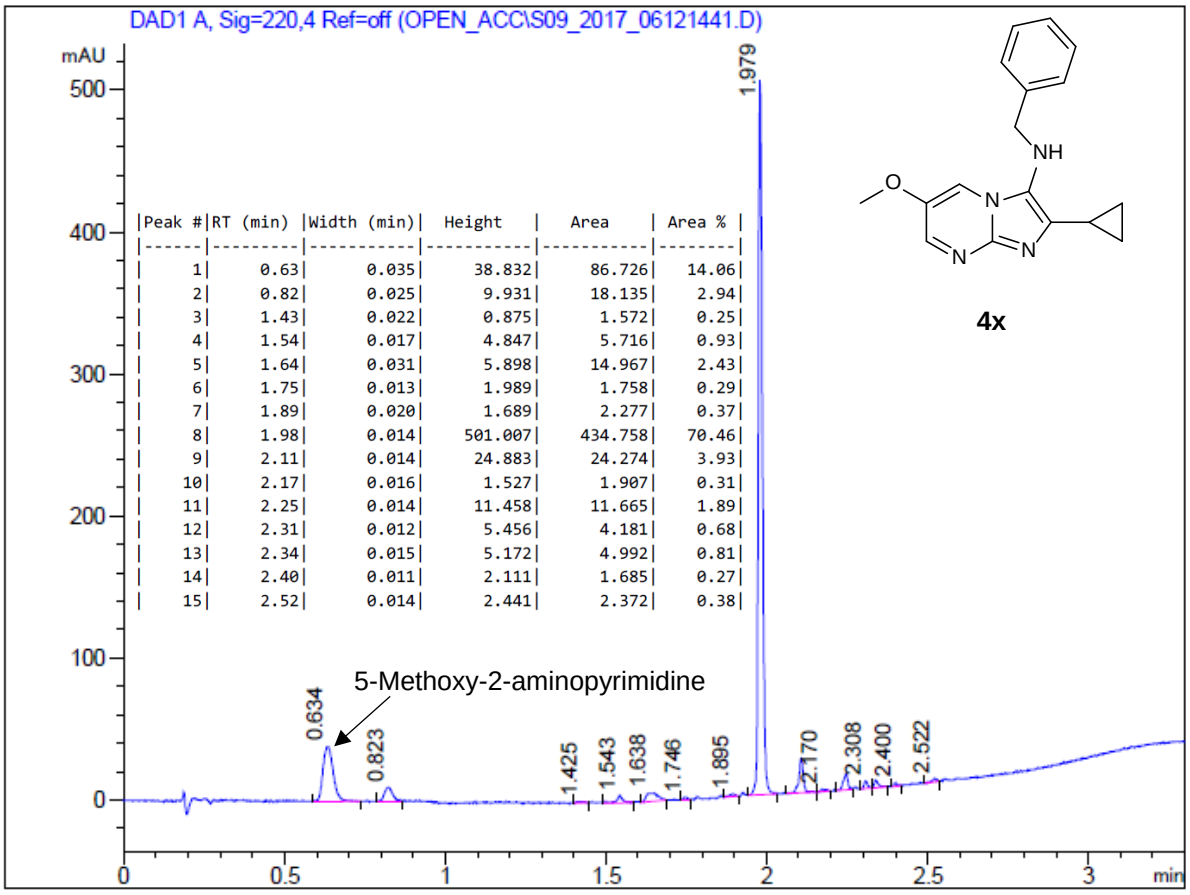
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	1.45	0.021	2.756	4.248	0.47
2	1.72	0.021	4.774	7.106	0.78
3	1.95	0.011	11.411	8.791	0.97
4	2.01	0.017	1.382	1.859	0.21
5	2.06	0.015	631.588	620.502	68.54
6	2.10	0.017	84.635	94.435	10.43
7	2.14	0.013	5.607	4.468	0.49
8	2.17	0.014	11.649	10.593	1.17
9	2.21	0.013	5.618	5.139	0.57
10	2.26	0.020	8.181	9.934	1.10
11	2.31	0.014	7.830	6.717	0.74
12	2.34	0.012	21.254	17.098	1.89
13	2.37	0.015	46.512	48.204	5.32
14	2.44	0.017	21.078	25.954	2.87
15	2.47	0.013	2.236	1.963	0.22
16	2.55	0.017	7.255	9.367	1.03
17	2.74	0.021	1.554	2.644	0.29
18	3.00	0.017	6.084	7.762	0.86
19	3.09	0.021	11.916	18.522	2.05



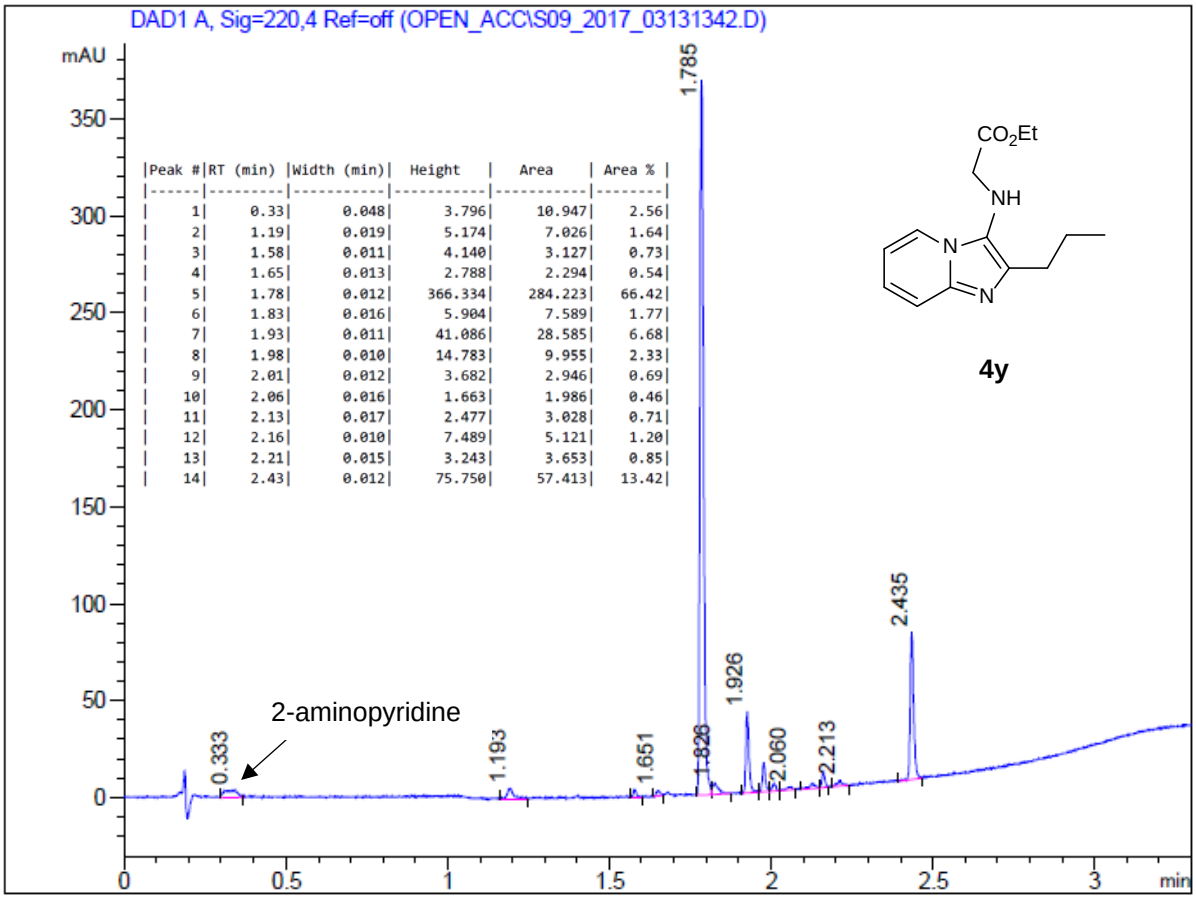
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.19	0.007	10.162	3.982	0.18
2	1.51	0.019	24.733	33.186	1.54
3	1.73	0.033	3.711	9.590	0.44
4	1.76	0.017	3.121	4.114	0.19
5	1.87	0.016	175.308	188.562	8.73
6	2.05	0.012	1.942	1.722	0.08
7	2.17	0.022	6.341	10.201	0.47
8	2.32	0.014	5.332	4.970	0.23
9	2.36	0.018	2.307	3.407	0.16
10	2.42	0.023	1207.553	1871.065	86.63
11	2.50	0.020	7.073	10.048	0.47
12	2.54	0.014	2.902	2.552	0.12
13	2.58	0.015	4.348	4.363	0.20
14	2.74	0.015	2.187	2.513	0.12
15	2.85	0.016	8.978	9.651	0.45



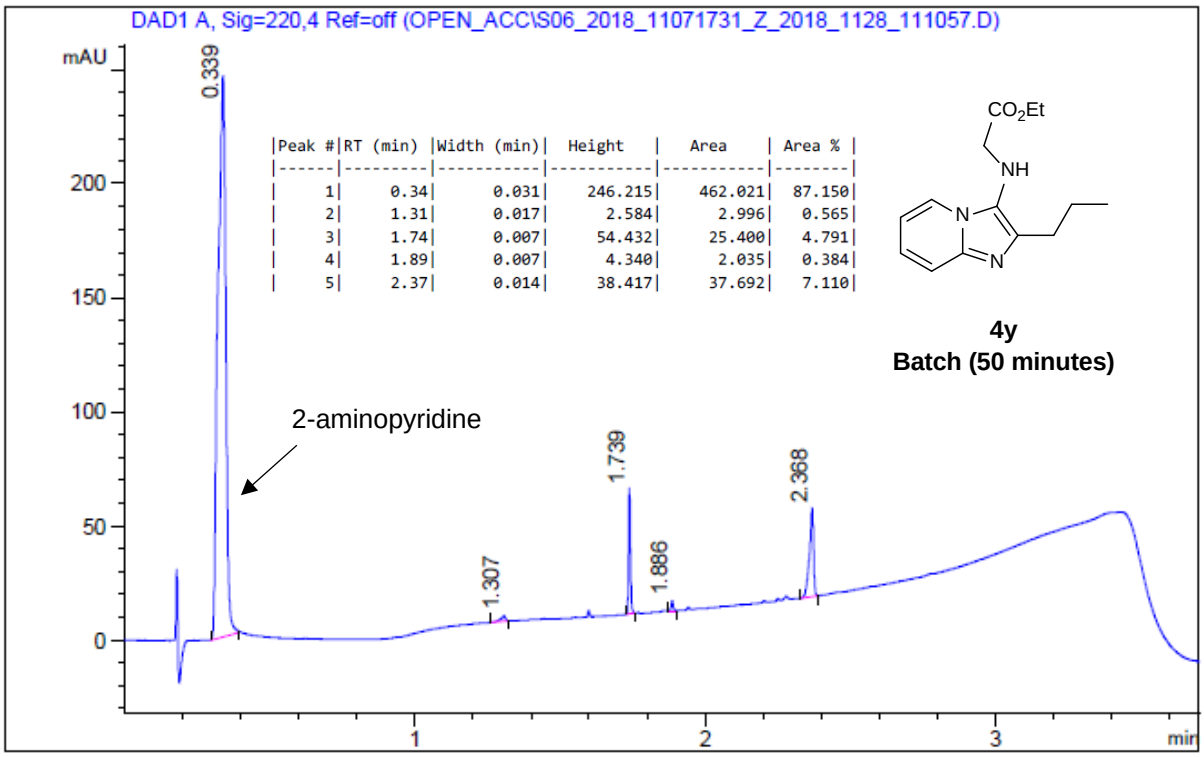
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.25	0.041	3.270	8.103	1.98
2	0.81	0.028	7.332	14.046	3.44
3	1.83	0.012	2.072	1.648	0.40
4	2.20	0.016	1.689	1.854	0.45
5	2.26	0.015	381.110	372.803	91.32
6	2.30	0.012	3.259	2.827	0.69
7	2.58	0.016	6.333	6.964	1.71



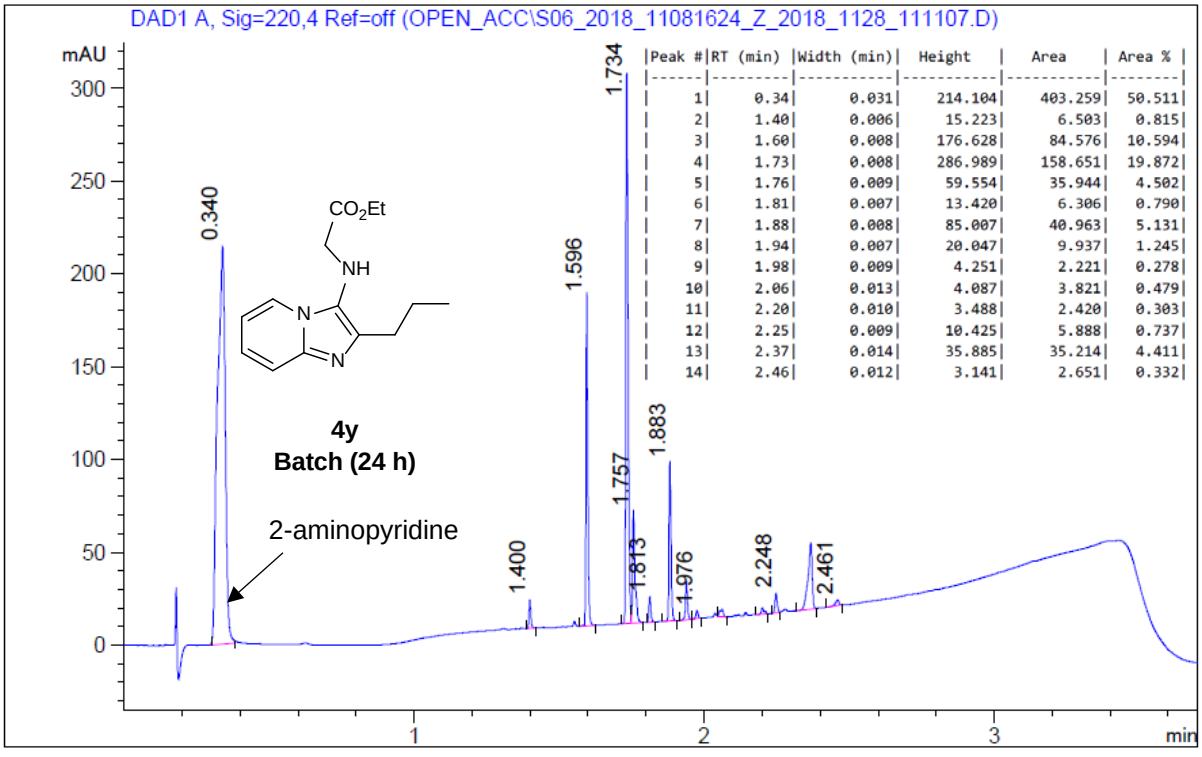
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.63	0.035	38.832	86.726	14.06
2	0.82	0.025	9.931	18.135	2.94
3	1.43	0.022	0.875	1.572	0.25
4	1.54	0.017	4.847	5.716	0.93
5	1.64	0.031	5.898	14.967	2.43
6	1.75	0.013	1.989	1.758	0.29
7	1.89	0.020	1.689	2.277	0.37
8	1.98	0.014	501.007	434.758	70.46
9	2.11	0.014	24.883	24.274	3.93
10	2.17	0.016	1.527	1.907	0.31
11	2.25	0.014	11.458	11.665	1.89
12	2.31	0.012	5.456	4.181	0.68
13	2.34	0.015	5.172	4.992	0.81
14	2.40	0.011	2.111	1.685	0.27
15	2.52	0.014	2.441	2.372	0.38



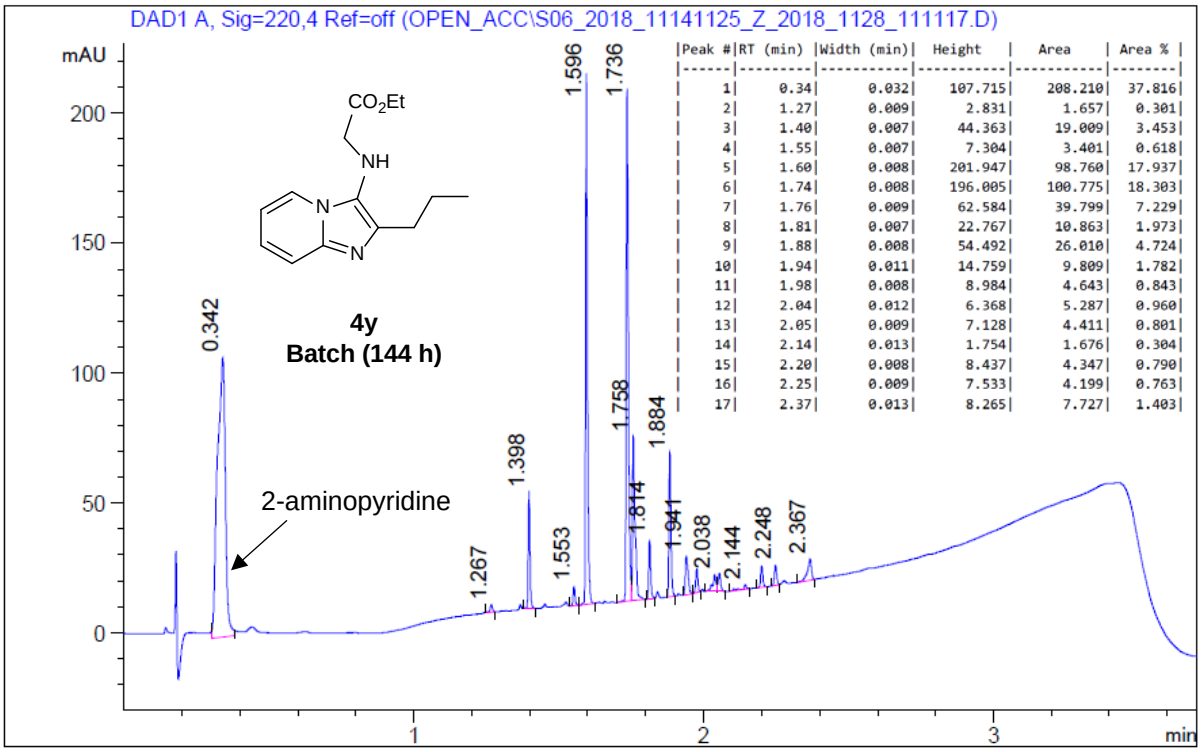
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.33	0.048	3.796	10.947	2.56
2	1.19	0.019	5.174	7.026	1.64
3	1.58	0.011	4.140	3.127	0.73
4	1.65	0.013	2.788	2.294	0.54
5	1.78	0.012	366.334	284.223	66.42
6	1.83	0.016	5.904	7.589	1.77
7	1.93	0.011	41.086	28.585	6.68
8	1.98	0.010	14.783	9.955	2.33
9	2.01	0.012	3.682	2.946	0.69
10	2.06	0.016	1.663	1.986	0.46
11	2.13	0.017	2.477	3.028	0.71
12	2.16	0.010	7.489	5.121	1.20
13	2.21	0.015	3.243	3.653	0.85
14	2.43	0.012	75.750	57.413	13.42



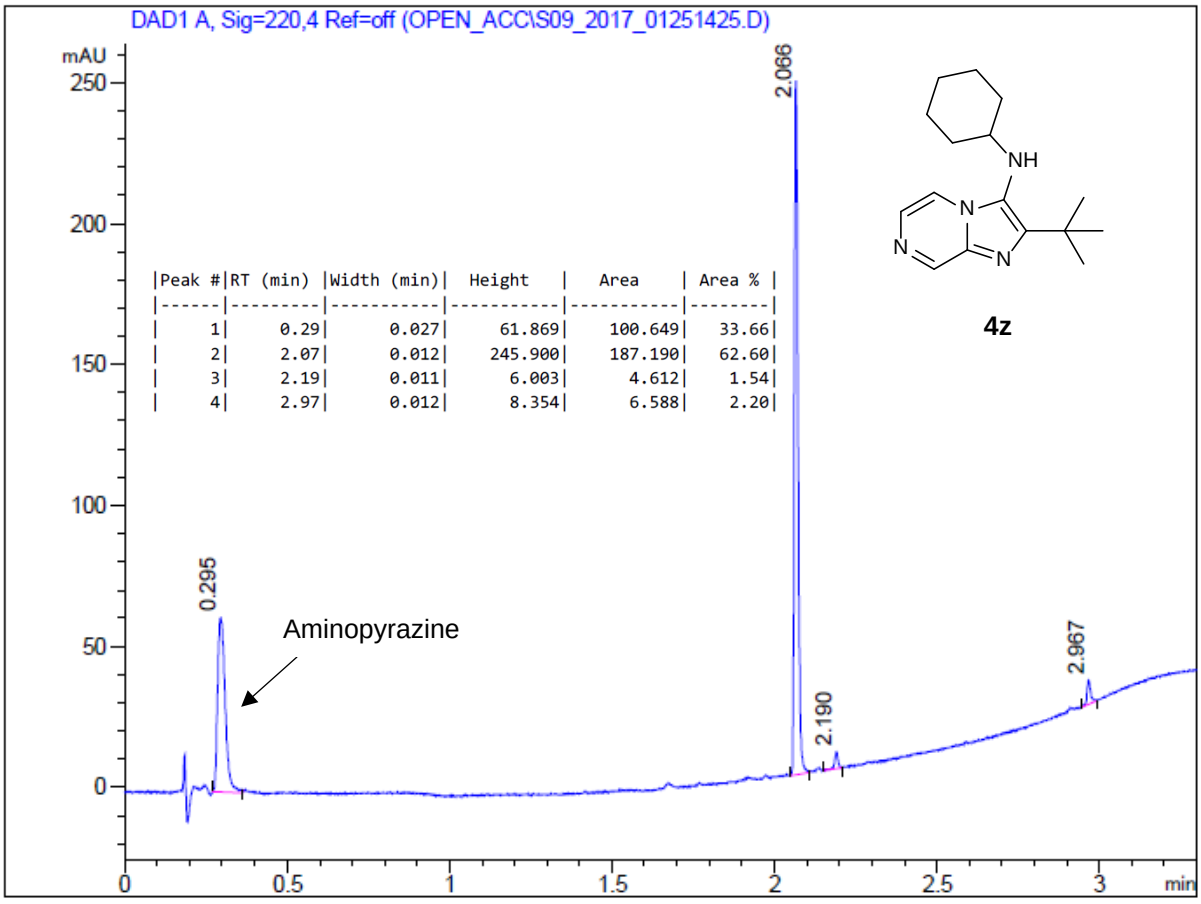
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.34	0.031	246.215	462.021	87.150
2	1.31	0.017	2.584	2.996	0.565
3	1.74	0.007	54.432	25.400	4.791
4	1.89	0.007	4.340	2.035	0.384
5	2.37	0.014	38.417	37.692	7.110



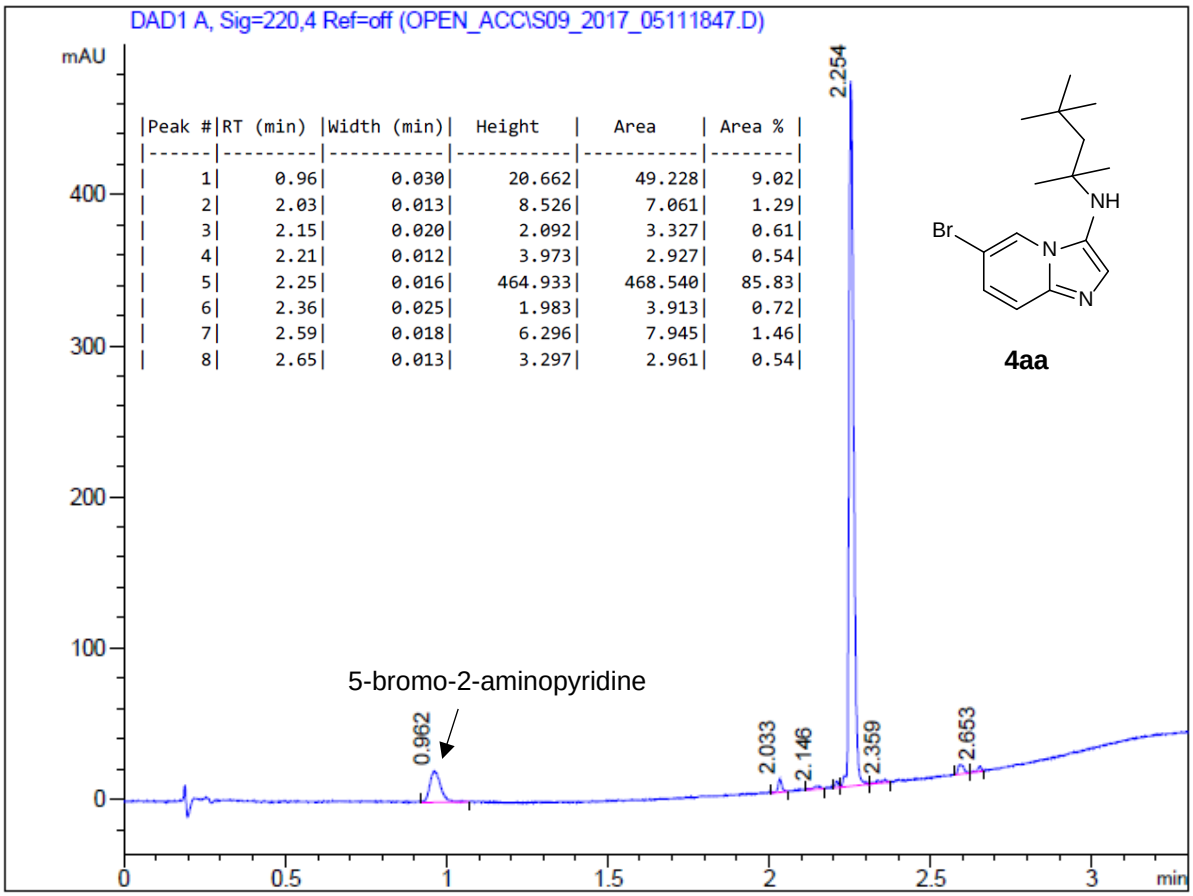
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.34	0.031	214.104	403.259	50.511
2	1.40	0.006	15.223	6.503	0.815
3	1.60	0.008	176.628	84.576	10.594
4	1.73	0.008	286.989	158.651	19.872
5	1.76	0.009	59.554	35.944	4.502
6	1.81	0.007	13.420	6.306	0.790
7	1.88	0.008	85.007	40.963	5.131
8	1.94	0.007	20.047	9.937	1.245
9	1.98	0.009	4.251	2.221	0.278
10	2.06	0.013	4.087	3.821	0.479
11	2.20	0.010	3.488	2.420	0.303
12	2.25	0.009	10.425	5.888	0.737
13	2.37	0.014	35.885	35.214	4.411
14	2.46	0.012	3.141	2.651	0.332



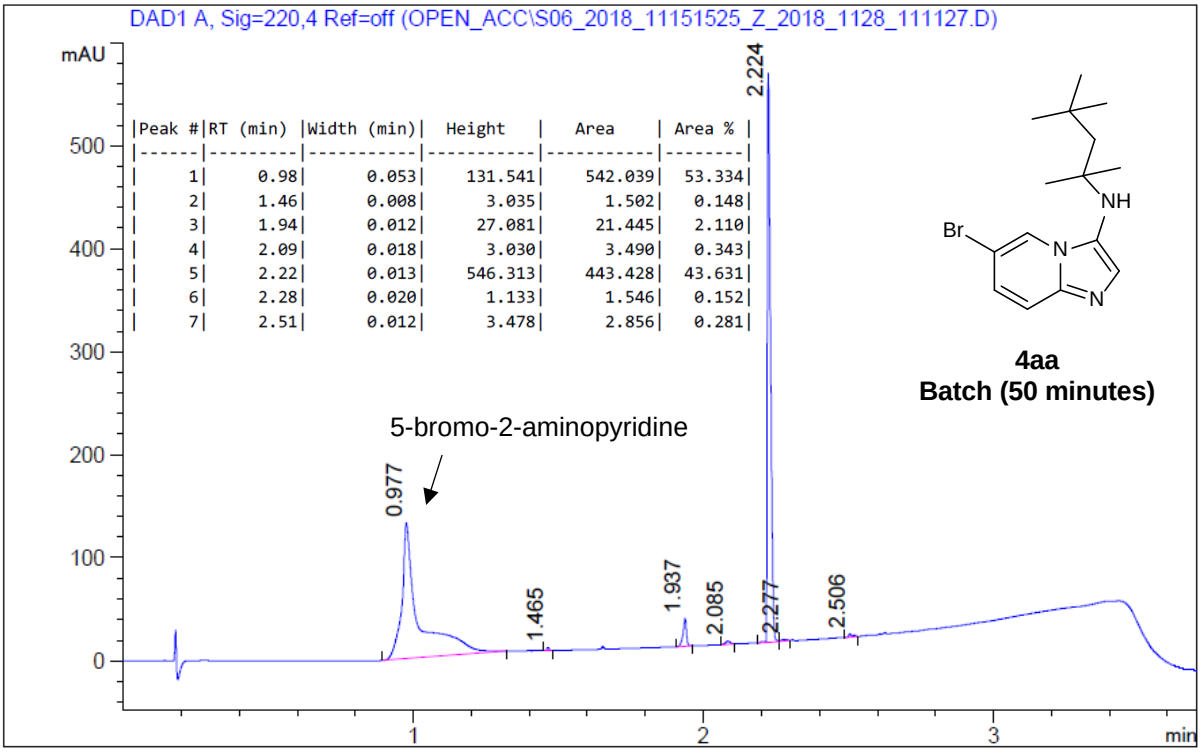
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.34	0.032	107.715	208.210	37.816
2	1.27	0.009	2.831	1.657	0.301
3	1.40	0.007	44.363	19.009	3.453
4	1.55	0.007	7.304	3.401	0.618
5	1.60	0.008	201.947	98.760	17.937
6	1.74	0.008	196.005	100.775	18.303
7	1.76	0.009	62.584	39.799	7.229
8	1.81	0.007	22.767	10.863	1.973
9	1.88	0.008	54.492	26.010	4.724
10	1.94	0.011	14.759	9.809	1.782
11	1.98	0.008	8.984	4.643	0.843
12	2.04	0.012	6.368	5.287	0.960
13	2.05	0.009	7.128	4.411	0.801
14	2.14	0.013	1.754	1.676	0.304
15	2.20	0.008	8.437	4.347	0.790
16	2.25	0.009	7.533	4.199	0.763
17	2.37	0.013	8.265	7.727	1.403



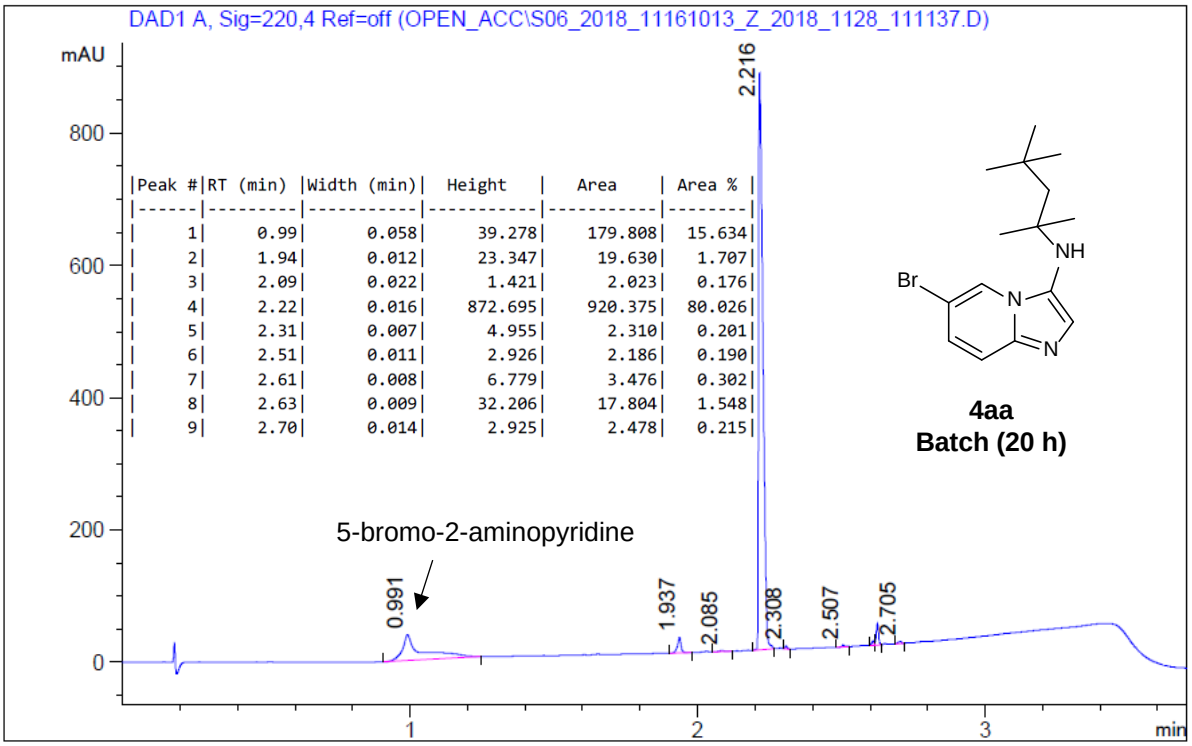
Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.29	0.027	61.869	100.649	33.66
2	2.07	0.012	245.900	187.190	62.60
3	2.19	0.011	6.003	4.612	1.54
4	2.97	0.012	8.354	6.588	2.20



Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.96	0.030	20.662	49.228	9.02
2	2.03	0.013	8.526	7.061	1.29
3	2.15	0.020	2.092	3.327	0.61
4	2.21	0.012	3.973	2.927	0.54
5	2.25	0.016	464.933	468.540	85.83
6	2.36	0.025	1.983	3.913	0.72
7	2.59	0.018	6.296	7.945	1.46
8	2.65	0.013	3.297	2.961	0.54



Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.98	0.053	131.541	542.039	53.334
2	1.46	0.008	3.035	1.502	0.148
3	1.94	0.012	27.081	21.445	2.110
4	2.09	0.018	3.030	3.490	0.343
5	2.22	0.013	546.313	443.428	43.631
6	2.28	0.020	1.133	1.546	0.152
7	2.51	0.012	3.478	2.856	0.281



Peak #	RT (min)	Width (min)	Height	Area	Area %
1	0.99	0.058	39.278	179.808	15.634
2	1.94	0.012	23.347	19.630	1.707
3	2.09	0.022	1.421	2.023	0.176
4	2.22	0.016	872.695	920.375	80.026
5	2.31	0.007	4.955	2.310	0.201
6	2.51	0.011	2.926	2.186	0.190
7	2.61	0.008	6.779	3.476	0.302
8	2.63	0.009	32.206	17.804	1.548
9	2.70	0.014	2.925	2.478	0.215

8. References

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